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[Intervention Review]

Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

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ABSTRACT

Background

Chronic heart failure (CHF) is a leading cause of morbidity and mortality worldwide. Anaemia is a common (12-55%) co-morbid condition and is associated with worsening symptoms and increased mortality. Anaemia is treatable and can be targeted in the treatment of patients with CHF. Erythropoiesis-stimulating agents (ESA), supplemented by iron therapy, are used to treat anaemia in chronic kidney disease and cancer, however safety concerns have been raised in these patients. The clinical benefit and safety of these agents in CHF remains unclear.

Objectives

To assess the benefits and risks of ESA for CHF patients with anaemia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2008, Issue 3), MEDLINE (1950 to October 2008), EMBASE (1980 to October 2008) and reference lists of articles. No language restrictions were applied.

Selection criteria

Randomised controlled trials of any ESA, with or without iron therapy, in CHF patients were eligible for inclusion.

Data collection and analysis

Three reviewers independently assessed study quality and extracted data. Original authors were contacted for additional information. The outcomes of interest were: exercise tolerance, haemoglobin level, New York Heart Association (NYHA) functional class, quality of life, left-ventricular ejection fraction, B-type natriuretic peptide, CHF-related hospitalisations, all-cause mortality and adverse effects. Risk ratios (RR) were calculated for dichotomous data and weighted mean difference (WMD) for continuous data.

Main results

Eleven studies (794 participants) were included. Overall quality of studies was moderate with nine studies being placebo-controlled but only five double-blinded. Compared to control, ESA treatment significantly improved exercise duration by 96.8 seconds (95% CI 5.2 to 188.4, p=0.04) and 6-minute walk distance by 69.3 metres (95% CI 17.0 to 121.7, p=0.009). Benefit was also noted in terms of peak VO2 (+2.29 mL/kg/min, p=0.007), NYHA class (-0.73, p<0.001), ejection fraction (+5.8%, p<0.001), B-type natriuretic peptide (-226.99 pg/mL, p<0.001) and quality-of-life indicators, with a mean increase in haemoglobin of 1.98 g/dL (p<0.0001). There was also a significantly lower rate of heart failure related hospitalisations (RR 0.62, 95% CI 0.44 to 0.87) and lower all-cause mortality (RR 0.61, 95% CI 0.37 to 0.99). No increase in adverse events with ESA therapy was observed, however studies were of small sample sizes and limited duration.

Authors' conclusions

Meta-analysis of small RCTs suggests that ESA treatment in patients with symptomatic CHF and mild anaemia (haemoglobin more than 10g/dL) can improve anaemia and exercise tolerance, reduce symptoms and have benefits on clinical outcomes. Confirmation requires well-designed studies with careful attention to dose, haemoglobin treatment target and associated iron therapy.

PLAIN LANGUAGE SUMMARY

Erythropoiesis-stimulating agents for people with chronic heart failure and anaemia

Chronic heart failure is a disorder in which the heart is unable to pump blood and deliver oxygen adequately throughout the body. Patients with heart failure may also suffer from anaemia, a condition of reduced red blood cells and diminished ability of the blood to carry oxygen. These patients appear to have worse symptoms and poorer survival and may benefit from additional therapy for their anaemia. Erythropoiesis-stimulating agents (ESAs) with iron supplements have been used since the 1980s to treat anaemia in chronic kidney disease and cancer patients. ESAs have the same action as erythropoietin, a hormone that is naturally produced by the kidneys to increase red blood cell production. This review shows that ESAs improves anaemia, exercise tolerance, quality of life and reduces symptoms in heart failure patients with a mild anaemia. ESAs may also reduce hospital admission and improve survival. There was no increase in major side effects in those receiving ESA therapy compared to control over the 2-12 month study period (maximum 12 months) although the effects of treatment over a longer period are not known. More research is needed to clarify the full effects and safety of ESAs as a treatment for anaemia in these patients.

BACKGROUND

Description of the condition

Chronic heart failure (CHF) affects over 23 million patients worldwide (Cleland 2001) and is a leading cause of morbidity and mortality. CHF is the end-stage result of common heart disorders including coronary artery disease, hypertension, cardiomyopathies and valvular heart disease, and is characterised by breathlessness, fatigue and fluid retention (ACC/AHA 2005). As CHF is primarily a disorder of the elderly, an ageing population will therefore contribute to an increasing prevalence of CHF. Patients frequently suffer from multiple non-cardiovascular comorbidities including pulmonary disease, thyroid disease, diabetes, renal insufficiency and anaemia.

Anaemia has recently been recognised as an important co-morbid condition which could be targeted in the overall management of CHF. Definitions of anaemia vary, although the World Health Organisation defines a haemoglobin level of less than 13.0 grammes per decilitre (g/dL) for men and less than 12.0 g/dL for women (Blanc 1968). Anaemia is common in CHF patients, with a prevalence of approximately 30% (Mitchell 2007) depending on the population studied and the level of haemoglobin considered. Multiple mechanisms associated with CHF may contribute to anaemia, including haemodilution, chronic kidney disease (CKD), activation of pro-inflammatory cytokines, and malnutrition (Felker 2004). Anaemia in people with CHF appears to be associated with worse symptoms, functional status and a poorer prognosis than in CHF patients without anaemia (Horwich 2002; Groenveld 2008). However anaemia as a cause of disease progres-

sion in CHF patients has yet to be established.

Description of the intervention

Routine medical management for CHF involves diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), beta-blockers, aldosterone antagonists and digoxin (ACC/AHA 2005). Although these treatments have reduced morbidity and mortality, overall hospital admissions for CHF continue to increase (Rosamond 2008) and new therapeutic pathways are being sought. Anaemia has emerged as a treatable comorbidity and has the potential to improve the prognosis of CHF.

Anaemia of chronic disease appears to be the most frequent cause of anaemia in CHF (Anand 2008) and may benefit from erythropoiesis-stimulating agents (ESAs) and iron therapy (Weiss 2005). ESAs currently available are darbepoetin alfa and two forms of recombinant human erythropoietin (rHuEPO), epoetin-alfa and epoetin-beta (Weiss 2005). There are also a range of supplementary iron preparations including oral iron (Shord 2008) and intravenous iron (Peeters 1996).

How the intervention might work

Darbepoetin alfa and rHuEPO have the same mode of action as endogenous erythropoietin (EPO) and are the first-line treatment for anaemia of CKD (NKF 2006) and cancer (EORTC 2007; ASCO/ASH 2008). Similarly, ESA treatment may improve CHF outcomes by alleviating symptoms associated with anaemia. Other benefits of ESAs studied in animal models include promoting cell survival during ischaemia-reperfusion injury (Parsa 2004) and stimulating blood vessel formation in the failing heart (Westenbrink 2007). However ESAs have been associated with adverse outcomes in CKD and cancer patients, with increased thromboembolic events, hypertension and mortality reported in patients dosed to higher haemoglobin targets (Henke 2003; Phrommintikul 2007; Bennett 2008).

Iron stores should be adequately maintained to ensure effective erythropoiesis; thus iron supplementation is recommended for patients with serum ferritin less than 100 mcg/L or serum transferrin saturation less than 20% (NKF 2006).

Why it is important to do this review

There are currently several strategies to identify and manage mild anaemia in CHF patients, but there are no definitive studies to guide clinical care and guidelines are inconclusive (ACC/AHA 2005; ESC 2008). Serious adverse events have reported in cancer and CKD patients, thus the safety profile of ESAs in CHF patients requires investigation. Several small randomised trials have evaluated ESA and iron therapy and larger randomised trials are ongoing. This review is required to summarise current evidence and provide clinical guidance while further definitive evidence is obtained.

OBJECTIVES

To assess the benefit and risk of ESAs for chronic heart failure patients with anaemia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Adult participants (over 18 years) with symptomatic CHF and anaemia of chronic disease. The definitions of CHF and anaemia of chronic disease used by each individual study were accepted.

Types of interventions

Any ESA with or without iron supplementation at any dose, duration, or mode of administration, compared to placebo or no treatment.

Types of outcome measures

Primary outcomes

1. Exercise tolerance as assessed by any functional capacity test, including treadmill exercise duration, the 6-minute walk test and peak VO2.

Secondary outcomes

1. Measure of anaemia correction: Change in haemoglobin (Hb) level.
2. New York Heart Association (NYHA) functional classification.
3. Quality of life (QoL).
4. Haemodynamic effects: Left ventricular ejection fraction (LVEF).

5. Disease progression: CHF-related hospital admissions and B-type natriuretic peptide (BNP).

6. All-cause mortality.

7. Adverse effects of specific interest including hypertension, stroke, myocardial infarction, and other thromboembolic effects.

Search methods for identification of studies

Electronic searches

An electronic search for relevant trials without language restriction was conducted on The Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, Database of Abstracts of Reviews of Effect and the NHS Economic Evaluation Database of *The Cochrane Library* (2008, Issue 3), MEDLINE (1950 to October 2008) and EMBASE (1980 to October 2008). The search strategies are listed in Appendix 1.

Searching other resources

Other resources included the reference lists of each identified study, other reviews, existing bibliographies and registers of ongoing trials including:

- Current Controlled Trials (www.controlled-trials.com)
- Clinical Trials register (www.clinicaltrials.gov)
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au)
- World Health Organisation International Clinical Trials Registry Platform (www.who.int/trialsearch).

Data collection and analysis

Selection of studies

The title and abstracts of studies retrieved by electronic searches were screened by one reviewer (KN) to determine eligibility for inclusion. The full text of a study was also considered where the title and abstract provided inadequate information for selection. Original authors were contacted for clarification of duplicate reports. Studies identified as potentially eligible were further assessed by several reviewers (DK, LM and MF). Reviewers were not blinded to authors of the studies. Any disagreements between reviewers were resolved by discussion.

Data extraction and management

Data extraction was conducted independently by three reviewers (KN, MF and DK), using a pre-tested data extraction form. Original authors were contacted where data were missing or unclear. When one study outcome was reported with two different analyses (e.g. adjusted versus unadjusted analysis), the unadjusted data were extracted.

Consensus data were entered into the Cochrane Collaboration software program Review Manager Version 5.0 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) for data analysis.

Assessment of risk of bias in included studies

Quality of included studies was independently assessed by three reviewers (KN, MF and DK) as part of the data extraction process using The Cochrane Collaboration's 'risk of bias' assessment tool (Higgins 2008a). The tool considers six domains of bias: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'. For each domain, the study method was described using verbatim quotes and judged for adequacy (Yes, No, Unclear). A judgement of 'Yes' indicated low risk of bias, while 'No' indicated high risk of bias. Disagreements of judgement were resolved by discussion. Sensitivity analyses were undertaken to determine the effects of study quality stratified by using the risk of bias domains.

Measures of treatment effect

Extracted data were entered into the Review Manager software and analysed by determining the risk ratio (RR) for dichotomous data and weighted mean difference (WMD) for continuous data. Ninety-five per cent confidence intervals (95% CI) and p-values were derived for all comparisons. In the text of this review, results are presented as WMD, 95% CI or RR, 95% CI unless stated otherwise.

Dealing with missing data

Original authors were contacted to obtain unreported data on study design, participant characteristics and selected outcome data. When missing data could not be obtained, imputation methods were used. Standard deviations (SD) for the end-of-study mean haemoglobin levels were imputed for two studies. One reported 'change in haemoglobin level' as median and interquartile ranges (IQR) (Ghali 2008). Given that the authors stated "data was approximately normally distributed" and the sample size was sufficiently large, the SD was imputed using the following formula: SD = IQR /1.35 (Higgins 2008b). The imputed SD was consistent with other studies. The other study (Cosyns 2008) did not provide SDs for the control group and we made the assumption that the SD for both control and ESA group were the same. Sensitivity analyses were later conducted to assess the effect of these assumptions.

Assessment of heterogeneity

For each outcome, a test of heterogeneity was explored using the Chi-squared test and I^2 statistic in the Review Manager software. The null hypothesis was for no heterogeneity of treatment effect. The Chi-squared test measures the deviation of observed effect sizes from an underlying overall effect. This test has low power at detecting true heterogeneity when studies have small sample size or are few in number, hence a p-value of 0.10 was used (Deeks 2008). The I^2 statistic assesses the impact of heterogeneity on the meta-analysis. The magnitude is roughly interpreted as:

- 0% to 40%: unimportant;
- 30% to 60%: represents moderate heterogeneity;
- 50% to 90%: represents substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity (Deeks 2008).

Assessment of reporting biases

A funnel plot and Egger's test was used to check for the presence of publication bias in analyses with fewer than ten studies (Egger 1997).

Data synthesis

When there was no evidence of statistical heterogeneity and pooling of results was clinically appropriate, a combined estimate was calculated using the fixed-effect model (Mantel 1959).

When statistically significant heterogeneity ($p<0.10$) was detected, several options were followed: the clinical diversity of studies was explored through pre-specified subgroup analyses comparing the different types of ESAs (darbepoetin alfa versus rHuEPO), the random effects model (DerSimonian 1986) was used, or the studies were not aggregated.

All analyses compared the ESA and control groups using a combination of endpoints scores or change from baseline scores for each outcome.

Outcomes assessed as continuous variables were exercise tolerance, NYHA class, LVEF, QoL and BNP. Exercise tolerance was analysed using exercise duration (seconds) and energy expenditure (peak VO2 by mL/kg/min) for maximal exercise protocols; and distance walked (metres) for the six-minute walk test (6MWT). Exercise duration was measured using the treadmill test and bicycle ergometry. Only results from the same exercise tolerance measure were combined: all maximal exercise tests and all 6MWT. Validated QoL instruments considered in the analyses were the Minnesota Living with Heart Failure Questionnaire (MLHFQ; Rector 1987), Kansas City Cardiomyopathy Questionnaire (KCCQ; Green 2000) and patient's global assessment (PGA; Packer 2002). MLHFQ and KCCQ change from baseline scores were assessed as separate continuous variables. A higher total score in the MLHFQ (range= 0 to 105) implies poorer QoL whereas a higher score in the KCCQ (range= 0 to 100) indicates improved QoL. PGA was assessed as a dichotomous variable with improvement versus no change or worsening of health status.

Outcomes assessed as dichotomous variables were CHF-related hospital admissions, all-cause mortality and adverse effects. Adverse effects of specific interest were hypertension, myocardial infarction, stroke and other thromboembolic effects, as adjudicated by the individual studies.

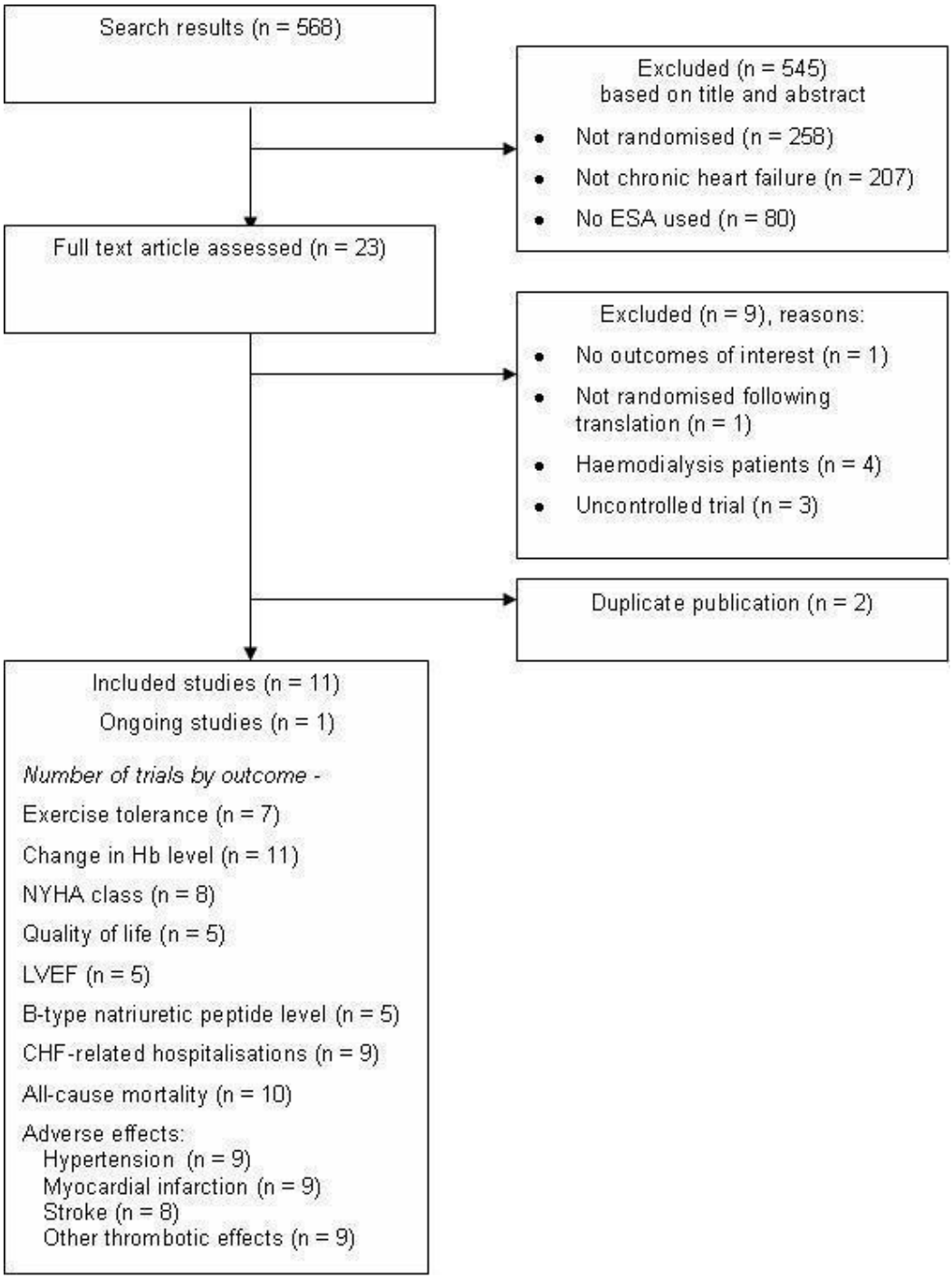
RESULTS

Description of studies

Results of the search

The search strategy yielded 568 results. Following screening of titles and abstracts, the full-text of 23 studies were further evaluated; of these, 11 studies with 794 participants met the inclusion criteria and one ongoing study was identified (Figure 1). Included studies were published from 2001 to 2008, the majority of trials were conducted in Europe and four trials declared pharmaceutical company sponsorship (Cleland 2005; Ponikowski 2007; van Veldhuisen 2007; Ghali 2008). Included and ongoing studies varied in sample size, duration, type of ESA, dosing regime and supplementary iron therapy. Details of studies included for review are shown in the Characteristics of included studies. Nine studies were excluded and reasons for exclusion are presented in the Characteristics of excluded studies. One ongoing study was identified and details are shown in the Characteristics of ongoing studies.

Figure 1. Flow diagram of study selection.



Included studies

Study design

All studies had a parallel design. One study (Cleland 2005) reported two separate trial protocols of which one ("Study 262") had a crossover design. No data from this sub-study was used in the meta-analysis. Palazzuoli 2006 and Palazzuoli 2007 were separate studies with different protocols (including different target haemoglobin and double-blind/ open-label follow-up periods). Mean study duration was 6.3 (SD 4.1) months, ranging from 2 months to 12 months. Of the 11 studies, three were multicentre (Ponikowski 2007; van Veldhuisen 2007; Ghali 2008) and the remaining eight were conducted at a single institution. Control arm was typically placebo with two studies (Silverberg 2001; Cosyns 2008) comparing ESA with no treatment.

Trial size

The largest trial (Ghali 2008) was a multicentre parallel study with 319 patients randomised to receive darbepoetin alfa or placebo. The smallest study recruited 15 patients (Mancini 2003).

Study population

All participants had symptomatic CHF, left ventricular (LV) systolic dysfunction (LVEF <40%) and anaemia (Table 1). Overall mean age ranged from 65-87 years and data from nine trials identified that 57% were men. All studies met the NYHA criteria for symptoms with a predominance of NYHA class III patients. Three studies included NYHA class I patients (Ponikowski 2007; van Veldhuisen 2007; Ghali 2008), where the inclusion criteria stipulated patients with "symptomatic CHF".

The most common aetiology of CHF was ischaemic heart disease (coronary heart disease and prior myocardial infarction) followed by dilated cardiomyopathy and hypertension. Two studies specified CHF secondary to ischaemic or idiopathic dilated cardiomyopathy in their inclusion criteria (Kourea 2008a; Parissis 2008).

Patient co-morbidities were not consistently reported. Severe valvular disease was an exclusion criterion in four studies (Cleland 2005; Palazzuoli 2006; van Veldhuisen 2007; Ghali 2008).

Participants were clinically stable receiving optimal CHF therapy with resting blood pressure less than 160/100mmHg. In three studies, participants were treated with maximally tolerated doses of CHF therapy for six months prior to trial commencement (Silverberg 2001; Palazzuoli 2006; Palazzuoli 2007). Baseline CHF medication was reported in six studies, including use of angiotensin-converting enzyme (ACE) inhibitors/ angiotensin receptor blockers (ARBs) (reported in five studies), beta-blockers (six studies), diuretics (four studies), digoxin (five studies), potassium-sparing agents (two studies), and vasodilators (two studies). The majority of participants in each trial were taking ACE inhibitors/ARBs and diuretics (range 91-92%). There was variation in the use of other concomitant medications including beta-blockers (range 40-91%), digoxin (range 31-93%), potassium-sparing agents (range 55-100%) and vasodilators (range 40-88%).

Baseline mean haemoglobin levels of participants ranged from 10.1 to 11.8g/dL. Multiple criteria for anaemia were used (Table 2) and studies attempted to exclude secondary causes of anaemia including acute or chronic bleeding and vitamin B12, folate levels and iron deficiency. Severe renal dysfunction was generally excluded, however two studies included patients with renal impairment (mean serum creatinine 2.4 to 2.5mg/dL) (Palazzuoli 2006; Palazzuoli 2007) and one study included patients with chronic renal disease (Cosyns 2008). Creatinine clearance was variably reported in five studies using Modification of Diet in Renal Disease and the Cockcroft-Gault formula (Cleland 2005; Palazzuoli 2007; Ponikowski 2007; van Veldhuisen 2007; Ghali 2008).

ESA intervention

ESAs were administered subcutaneously to all participants but were titrated to haemoglobin targets ranging from 11.5 to 12g/dL to 13 to 15g/dL. The type of ESA and dose-regimen used in the studies varied. Darbepoetin alfa was used in six studies and rHuEPO in five studies. Darbepoetin alfa starting doses ranged from 0.75 to 5.0mg/kg. In two darbepoetin alfa studies (Cleland 2005; van Veldhuisen 2007), several dosage arms were compared to one control group. Although van Veldhuisen 2007 compared a fixed starting dose of 50μg and weight-based starting dose of 0.75μg/kg with a control group, data from the two treated groups were combined for the analysis. Cleland 2005 compared three different dosage arms (2.0, 3.0 and 5.0μg/kg) with control in one sub-study ("Study 198"), however only data from the 2.0μg/kg group could be analysed.

Schemes for administration ranged from once every two days to once every 29 days. Darbepoetin alfa was administered every 14 days (Ponikowski 2007; van Veldhuisen 2007; Ghali 2008), 20 days (Kourea 2008a; Parissis 2008) or 29 days (Cleland 2005). For rHuEPO, dosing regimes were 4000U weekly (Silverberg 2001), 5000U thrice-weekly (Mancini 2003), or 6000IU twice-weekly (Palazzuoli 2006; Palazzuoli 2007). Thus, the cumulative weekly dose for rHuEPO ranged from 4,000U to 15,000U per week.

Iron as a co-intervention

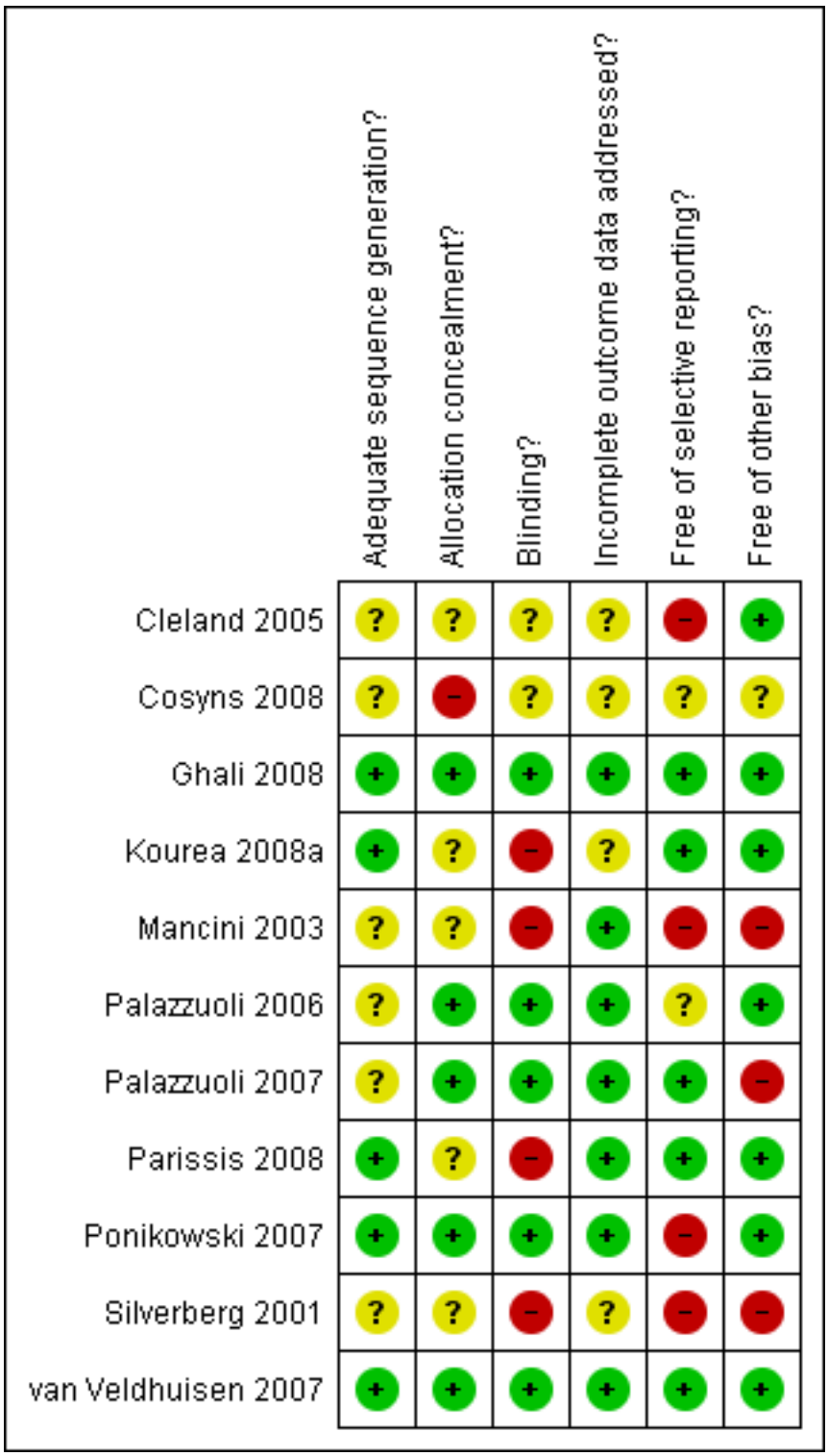
Supplementary iron therapy was provided by all except two studies (Cleland 2005, Cosyns 2008). Iron was provided as part of

fixed treatment (Silverberg 2001; Mancini 2003; Palazzuoli 2006; Palazzuoli 2007; Kourea 2008a; Parissis 2008) or unless baseline ferritin was more than 800ng/mL (Ponikowski 2007; van Veldhuisen 2007; Ghali 2008). Of the nine studies providing iron therapy, one study administered ferric sucrose intravenously (Silverberg 2001), while the other studies administered iron preparations orally. One study also prescribed folate (1mg daily) as an additional co-intervention to the treatment group (Mancini 2003).

Risk of bias in included studies

The individual assessment for each study is shown in the 'Risk of bias' table (see Characteristics of included studies) and chart (Figure 2). Adequate generation of the randomisation sequence was found in six studies. In general, concealment of allocation was poorly reported but was judged to be adequate in five studies including 77% of the study participants (n= 616). Blinding was variable: five studies were double-blinded, three studies had only outcome assessors blinded, two studies did not adequately report methods and one study was not blinded. Out of the 11 studies, only two studies were not placebo-controlled (Silverberg 2001, Cosyns 2008). Regarding incomplete outcome data, most of the studies were short term so the loss to follow-up was low. Withdrawals and associated reasons were reported in five studies. There was limited evidence of selective outcome reporting. The four studies that were judged to be inadequate in this domain had not specified their primary outcomes and one study did not specify the follow-up period, which ranged from 5 to 12 months (Silverberg 2001).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



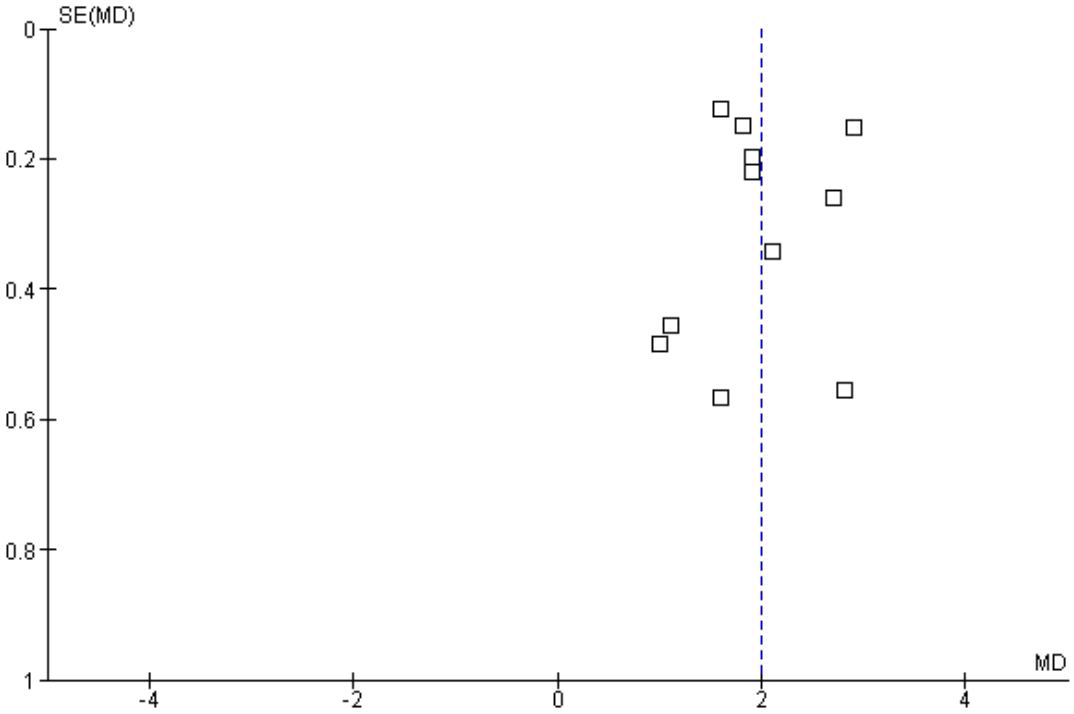
Another potential source of bias was imbalance in baseline characteristics between groups. In one study, the ESA group had more diabetics and less use of beta-blockers than control (van Veldhuisen 2007). In another study, the ESA group had greater distance on the 6MWT at baseline (405m versus 321m) (Mancini 2003). However it was difficult to assess the similarity of study groups at baseline as most studies did not include tests for statistical significance of baseline differences.

The type of publication also influenced quality of outcome reporting. Ten studies were published as full text papers in print journals and one study was published as a letter to the editor (Cosyns 2008).

Publication bias

Only one meta-analysis could be accurately assessed for funnel plot asymmetry, as all other comparisons included less than ten studies. Analysis of data reported for change in haemoglobin level detected a statistically significant asymmetric distribution of studies (p=0.042; Figure 3). This may suggest that negative results were underreported, however cautious interpretation of these statistics should be made in view of the high heterogeneity identified which may also explain the asymmetry noted (Terrin 2005).

Figure 3. Funnel plot of comparison: 1 ESA versus control, outcome: 1.7 Change in haemoglobin level (g/dL).



Effects of interventions

1. Exercise tolerance

The primary outcome of exercise tolerance was reported in seven studies including 623 participants (Analysis 1.3). Meta-analyses of all exercise tolerance outcomes had wide confidence intervals and a random effects model was applied. Overall, exercise duration improved by 15% from baseline, distance walked by 19% and peak VO2 by 12% in those treated with ESAs.

1.1 Exercise duration

Exercise duration was measured in 362 participants (four studies) and improved by 96.82 seconds (95% CI 5.22 to 188.42, p=0.04) compared to placebo.

1.2 Distance on 6MWT

Distance on the 6MWT was measured in 261 participants (four studies) and the overall weighted mean difference (WMD) was 69.33 metres comparing ESA with control (95% CI 16.99 to121.67, p=0.009).

1.3 Peak VO2

Peak VO2 was measured in 102 participants (three studies) and improved by 2.29mL/kg/min (95% CI 0.62 to 3.95, p=0.007) (Analysis 1.4). Sensitivity analysis was carried out excluding one study (Mancini 2003) that had measured peak VO2 using bicycle exercise, but this had no significant effect on the pooled analysis. Peak VO2 at anaerobic threshold was also measured by two studies (Mancini 2003; Palazzuoli 2006). In 61 participants, the anaerobic threshold increased by 2.29mL/kg/min in favour of treatment (95% CI 0.09 to 5.75, p=0.04).

2. Change in haemoglobin level

All 11 studies reported change in haemoglobin level and 782 participants were meta-analysed. There was a clinically and statistically significant increase in haemoglobin level of 1.98g/dL in participants treated with ESAs (95% CI 1.62 to 2.35, p<0.0001; Analysis 1.6). Sensitivity analyses excluding studies with imputed data (Cosyns 2008; Ghali 2008) had no effect on the pooled analysis.

3. NYHA functional class

Eight studies including 657 participants reported change in NYHA class from baseline until end of study. There was a statistically significant improvement in NYHA class, which changed by -0.73 (95% CI -1.11 to -0.36, p=0.0001), suggesting a reduction in CHF symptoms in those treated by ESAs (Analysis 1.8). One study reported change in NYHA class at 4 months and at 12 months (Palazzuoli 2007), however results were similar for both time periods.

4. Quality of life

Quality of life was assessed by the KCCQ, MLHFQ and PGA. KCCQ scores were reported by three studies including 247 participants. Changes in the overall summary score (WMD 4.60, 95% CI 0.46 to 8.75, p=0.03; Analysis 1.9) and the clinical summary score were statistically significant (WMD 7.10, 95% CI 2.77 to 11.43, p=0.001; Analysis 1.10). Change in the MLHFQ total score was reported in three studies including 462 participants and PGA was reported in four studies including 548 participants. Trend towards improvement in MLHFQ was non-significant (Analysis 1.11) but the PGA was significantly improved with RR 1.16 (95% CI 1.02 to 1.32, p=0.02; Analysis 1.12).

5. Disease progression

5.1. LVEF

Five studies including 321 participants reported LVEF, which improved by 5.77% compared to control (95% CI 2.43 to 9.11, p= 0.0007; Analysis 1.13).

5.2. BNP

BNP levels were measured in 203 participants (five studies) and decreased by 226.99pg/mL compared to control (95% CI -322.68 to -131.29, p<0.00001; Analysis 1.14).

6. CHF-related hospitalisations

Nine studies including 734 participants were analysed. CHF-related hospitalisation occurred in 48 of 412 participants in the ESA groups compared to 66 of 322 participants in the control groups. CHF-related hospitalisation was significantly reduced by 38% with ESA intervention (RR 0.62, 95% CI 0.44 to 0.87, p= 0.005; Analysis 1.15).

7. All-cause mortality

Ten studies including 764 participants identified a significant reduction in all-cause mortality associated with ESA treatment; RR 0.61 (95% CI 0.37 to 0.99, p=0.04; Analysis 1.16). Deaths occurred in 25 of 426 participants in the ESA groups compared to 35 of 338 participants in the control groups. Causes of death included progressive CHF, sudden death, pneumonia, mitral valve surgery and ischaemic heart disease.

8. Adverse effects

Adverse effects of specific interest including hypertension, stroke, myocardial infarction and other thromboembolic effects were rare. Overall, there were no statistically significant differences between groups.

8.1. Hypertension

Nine studies including 741 participants were analysed. Hypertension, as specified by each study, occurred in 18 of 410 participants in the ESA groups compared to 12 of 331 participants in the control groups. An increased relative risk of hypertension was not statistically significant; RR 1.31 (95% CI 0.67 to 2.54, p= 0.43; Analysis 1.17).

8.2. Stroke

Eight studies including 700 participants were analysed. Incidence of stroke was reported in 7 of 389 participants in the ESA groups and 4 of 311 participants in the control groups. There was no statistically significant increase in risk between groups; RR 1.57 (95% CI 0.52 to 4.70, p=0.42; Analysis 1.18).

8.3. Myocardial infarction

Nine studies including 732 participants were analysed. Incidence of myocardial infarction was reported in 9 of 410 participants in the ESA groups and 12 of 322 participants in the control groups. There was no statistically significant increase in risk between groups; RR 0.69 (95% CI 0.31 to 1.55, p=0.37; Analysis 1.19).

8.4. Other thromboembolic effects

Nine trials including 741 participants were analysed. Thromboembolic events were reported in 4 of 410 participants in the ESA groups and 6 of 331 participants in the control groups. There was no statistically significant increase in risk between groups; RR 0.65 (95% CI 0.22 to 1.88, p=0.42; Analysis 1.20).

Heterogeneity

There was substantial heterogeneity between the trials for exercise tolerance measures, change in haemoglobin level, NYHA class and LVEF ($p<0.10$, $I^2>60\%$). No evidence of heterogeneity was found for CHF-related hospitalisations, all-cause mortality or adverse effect outcomes ($p>0.10$, $I^2 = 0\%$).

The small number of studies precluded subgroup and sensitivity analyses for most of the outcomes to explore heterogeneity. Subgroup analyses comparing types of ESA used was undertaken for the change in haemoglobin level (Analysis 1.7). Darbepoetin alfa was used in six studies with 610 participants, which increased haemoglobin level by 1.74g/dL (95% CI 1.28 to 2.20, p=0.001). Within this subgroup, substantial heterogeneity remained ($Chi^2 =16.22$, p=0.003, $I^2 =75\%$) due to one study that showed marked effect of treatment (Cleland 2005). Recombinant human EPO was used in five studies with 172 participants and increased haemoglobin level by 2.26 g/dL (95% CI 1.71 to 2.81, p<0.0001). There was little evidence of heterogeneity between trials in the rHuEPO subgroup ($Chi^2=3.06$, p=0.22, $I^2=35\%$).

DISCUSSION

Summary of main results

The principal finding of this systematic review was that improvement of anaemia with ESA treatment in participants with CHF and mild anaemia was associated with improved LV function, improved exercise tolerance and reduction in CHF symptoms. There was an overall reduction in clinical outcomes and the treatment was well tolerated.

This study confirms that ESAs effectively raise haemoglobin levels in anaemic CHF patients. ESAs are established treatments for anaemia in chronic kidney disease (CKD) patients and cancer patients undergoing chemotherapy, based on the evidence of an absolute or relative defect in erythropoietin production. However, the pathogenesis of anaemia in CHF is multifactorial. Causes of anaemia implicated in CHF include inflammation, CKD, absolute iron-deficiency, ACE inhibitor use, chronic blood loss, malnutrition and plasma volume overload (Okonko 2004). In this review we have evaluated the effect of ESAs in patients with CHF and anaemia without an identifiable secondary cause. The studies examined excluded patients with low iron indices, folate or vitamin B12 deficiency, serum creatinine greater than 3mg or any co-morbid conditions known to cause anaemia. All participants suffered from a 'mild' anaemia with baseline haemoglobin levels ranging from 10.1 to 11.8g/dL, although the criteria for anaemia varied between trials. Thus ESAs yielded positive haematological response in the absence of a treatable cause of anaemia.

ESA treatment improved exercise tolerance, which was the primary outcome of this study. This effect was clinically signficant across maximal (exercise duration) and submaximal exercise performance (distance on six-minute walk). Exercise duration improved by 96.88 seconds (95% CI 5 to 188, p=0.04). In comparison, a meta-analysis investigating ACE inhibition on exercise duration in CHF patients showed an improvement of 28 seconds (95% CI 12 to 45, p<0.001; Abdulla 2004). Distance walked improved by 69 metres (95% CI 17 to 122, p=0.009), greater than a distance of 54 metres considered sufficient for a noticeable functional improvement (Redelmeier 1997). Exercise limitation is a cardinal symptom in CHF patients. While routine CHF therapies confer mortality and morbidity benefits, their effects on exercise capacity are mixed. ACE inhibitors are known to improve exercise capacity, but beta-blockers have not demonstrated consistent results (MacMahon 1997). The effect of ESAs on exercise tolerance is consistent with raised haemoglobin levels and increased oxygen delivery to the periphery. Similarly, treatment with rHuEPO in haemodialysis patients improved peak VO2, anaerobic threshold and maximal workload (Mayer 1988; McMahon 1992). This study also found that ESAs improved symptoms, as evidenced by a reduction in NYHA functional class. Thus, exercise capacity changes associated with ESA treatment were reflected by a benefit in symptoms.

Quality of life assessed using MLHFQ, KCCQ and PGA was improved with ESA treatment. KCCQ overall summary score and clinical summary score improved, although a change of five points is considered clinically significant (Spertus 2005). Treatment effect using the MLHFQ did not reach statistical significance and may be explained by lower sensitivity of the MLHFQ compared to the KCCQ to measuring clinical change (Green 2000). Several retrospective studies in CHF patients have reported that lower haemoglobin levels are associated with lower NYHA class and poorer QoL (Horwich 2002; Falk 2006; Tin 2006). However, Kosiborod 2008 found no significant association between change in haematocrit and KCCQ overall scores after three months in patients with CHF and mild-moderate anaemia (baseline haematocrit <33-39%). This study investigated CHF patients following myocardial infarction compared to patients with chronic stable CHF in our review. The positive effect of ESAs on QoL in cancer and CKD patients is well-documented (Ross 2003). A Cochrane review of 3,670 cancer patients found ESAs improved cancer-specific QoL measures, particularly anaemia-related fatigue (Bohlius 2006a). In haemodialysis patients, disease-specific and generic QoL measures also showed benefit from rHuEPO (Laupacis 1991; Besarab 1998).

The potential mechanistic benefits of ESAs in CHF patients including improved exercise tolerance and LVEF can be compared to the effects of established treatments in CHF. ESAs increased LVEF by 5.77% (95% CI 2.43 to 9.11, p=0.0007), which is comparable to results with beta-blockers showing dose-related improvements of 5% to 10% (Bristow 1996; Colucci 1996; MacMahon 1997). Improvement in LVEF was associated with a beneficial neurohormonal response, assessed by significant reduction of BNP levels. In CKD patients, anaemia is considered an independent risk factor for LV hypertrophy (Levin 1999), but controlled trials investigating the effect of ESAs on regression of hypertrophy have produced inconsistent results (Foley 2008). The mechanism by which ESAs benefit cardiac function is not fully understood. In severe anaemia (haemoglobin less than 10g/dL), neurohormonal activation causes fluid retention and LV remodeling in the long-term (Metivier 2000). LV hypertrophy and myocardial cell death contributes to systolic dysfunction (Anand 1993). In CHF patients, a retrospective substudy of 69 CHF patients found that a 1g/dL spontaneous increase in haemoglobin level was associated with a 4.1g/m^2 decrease in LV mass although not related to LVEF (Anand 2004). LVEF is affected by ventricular volumes, preload, afterload, heart rate and valvular function and these haemodynamic variables are also affected by anaemia. ESAs may reduce ventricular loading and prevent structural changes through the improvement of anaemia and neurohormonal alteration. Further, the cytoprotective effect of ESAs on myocardial cells and vascular endothelium demonstrated in animal models deserve further clarification in terms of benefits for the failing myocardium (Maiese 2005; Westenbrink 2007).

For clinical outcomes, ESAs were associated with a reduction in HF-related hospital admissions by 38% and all-cause mortality by 39% (absolute reduction of 4.5%). Beneficial effects on hospitalisation have also been confirmed in a smaller meta-analysis of seven trials (van der Meer 2009). This is comparable to other HF treatments with ACE inhibitors lowering the risk of hospital readmission by 23% (odds ratio 0·73, 0·63 to 0·85, p<0·0001) and mortality by 20% (odds ratio 0·80, 0·74-0·87, p<0·0001) (Flather 2000). Treatment with digoxin produces a risk reduction in hospitalisation of 28% (RR 0.72, 0.66 to 0.79, p=0.001), although digoxin does not confer any mortality benefit (DIG 1997). However, trials included in this review were not adequately powered, or of sufficient duration, to evaluate mortality and assessed deaths as a safety end point. Evidence for all-cause mortality was based on 60 deaths out of 764 participants (7.9%). Nevertheless, benefit in clinical outcomes associated with improvements in LV function suggest the observations are not due to chance.

This analysis found no apparent effect on hypertension, stroke, myocardial infarction or other thromboembolic effects although our ability to detect a small increase (or decrease) in the hazard ratio was limited by the small sample size and short-term follow-up. A pooled safety analysis of individual patient data from three of the included studies using darbepoetin alfa (Ponikowski 2007; van Veldhuisen 2007; Ghali 2008) also showed no difference in adverse effect profile between treatment and control groups (Klapholz 2008). Adverse effects noted in cancer and CKD patients have not been observed in CHF patients and may be related to the different disease process. Meta-analyses of cancer patients randomly assigned ESA therapy or placebo for anaemia found an increased risk of thromboembolic complications by 67% (RR 1.67, 95% CI 1.35 to 2.06, p<0.001; Bohlius 2006), and 1.10-fold increase in mortality (hazard ratio 1.10, 95% CI 1.01 to 1.20, p=0.03) (Bennett 2008). Similarly, a meta-analysis of 5143 CKD patients treated with rHuEPO to different target haemoglobin levels found increased all-cause mortality (RR 1.17, 95% CI 1.01 to 1.35, p=0.031), arteriovenous access thrombosis (RR 1.34, 95% CI 1.16 to 1.54, p=0.0001) and poorly controlled hypertension (RR 1.27, 95% CI 1.08 to 1.50, p=0.004) (Phrommintikul 2007). These adverse effects occurred in patients that were dosed to higher haemogloblin levels of 12-16g/dL compared to lower targets. Taken together, excess adverse effects were observed in CKD and cancer trials with higher target haemoglobin levels. The proposed mechanisms for cardiovascular events is through thrombotic and hypertensive risk (Taylor 1992). However, a recent randomized placebo-controlled trial of 4038 CKD patients with type 2 diabetes and mild anaemia dosed with darbepoetin alfa to a target haemoglobin of 13g/dL found an increased risk of stroke which appeared to be independent of any increase in blood pressure (hazard ratio 1.92, 95% CI 1.38 to 2.68, P<0.001), with no apparent difference in risk of myocardial infarction, CHF, hospitalisation for myocardial ischaemia or mortality between groups (Pfeffer 2009). Whether adverse effects are related to the higher haemoglobin target levels, or higher doses of ESA used to achieve

these targets, has yet to be evaluated in CHF patients.

This review found no excess adverse effects in the treatment group although included studies had haemoglobin targets ranging from 11.5 to 15g/dL. This may be due to short follow-up time of the studies and differences between CHF patients compared to renal and oncology patients (e.g. different comorbidities, concomitant therapies and aetiology of anaemia). The Reduction of Events With Darbepoetin Alfa in Heart Failure Trial (RED-HF 2008) is a multicentre RCT that should inform the debate. RED-HF 2008 will investigate a composite outcome of mortality and first hospital admission for worsening CHF in 2,600 CHF patients. Similar to characteristics of participants in this review, the RED-HF 2008 eligibility criteria for CHF participants are NYHA class II-IV and LVEF $\leq$ 40% and anaemia defined by a haemoglobin level of 9-12g/dL. As the study will titrate the ESA dose to a haemoglobin level of 13g/dL, the optimal haemoglobin level to be achieved in anaemic CHF patients has yet to be addressed.

Potential biases in the review process

These findings should be interpreted in light of limitations associated with meta-analysis. There was heterogeneity of study quality, with two studies not placebo-controlled (Silverberg 2001; Cosyns 2008). Monitoring or reporting of adverse effects was also limited. Variation between trials was apparent in terms of characteristics of participants, interventions and methods.

Although different types of ESAs and dosing regimes were used, darbepoetin alfa and rHuEPO showed equal efficacy in subgroup analyses. This is consistent with guidelines in CKD and cancer that consider a class effect (NKF 2006; ASCO/ASH 2008). ESAs were used in combination with iron therapy in most included studies. However the effect of iron supplementation, route of iron administration (oral versus intravenous) and different iron agents could not be clarified due to the small number of studies. Although trials of intravenous iron alone have shown positive effects in CHF patients with transferrin saturation less than 15% (Bolger 2006b; Toblli 2007; Okonko 2008), this analysis included participants considered iron replete with transferrin saturation more than 15%. Concomitant iron therapy reduces the dose of ESAs and prevents functional iron deficiency associated with increased rates of erythropoiesis in CKD and cancer patients (Auerbach 2004; NKF 2006). As iron therapy has been associated with adverse outcomes in patients with high or normal ferritin levels (Weiss 2005), there is a need to clarify when to initiate and cease iron administration.

These effects were achieved with concurrent optimal CHF therapy, including ACE inhibitors or ARBs and beta-blockers. Established CHF therapies affecting the renin-angiotensin system have been implicated in the pathogenesis of anaemia (Tang 2006). However baseline CHF medication was not well reported in included studies and potential interactions could not be adjusted for in our analyses.

Functional capacity tests varied from maximal (treadmill test, bicycle ergometer) to submaximal tests (6MWT) along with the outcome measures. Results from treadmill and bicycle testing were combined in the meta-analyses of exercise duration and peak VO2. However, treadmill testing yields 10% higher peak VO2 and longer exercise duration than bicycle ergometry (Page 1994; Kim 1999). Sensitivity analyses showed the statistically significant effect on exercise duration produced by bicycle was not evident on treadmill, but peak VO2 results were the same. Within studies, exercise testing can be affected by psychological factors such as coaching, encouragement from test personnel and differences in patient's tolerability (Guyatt 1985; ESC 2008). Variability in test conduct across centres may explain the lack of exercise duration improvement in the largest multicentre study (Ghali 2008). Information regarding exercise test standardisation was generally limited and may have introduced bias to results: Ghali 2008 conducted at least two baseline screening tests and assessed level of exertion using the Borg scale, and Palazzuoli 2006 only included patients who reached their anaerobic threshold. Distance on 6MWT was measured in four studies, but only one study reported that encouragement was not used (Mancini 2003).

Statistical heterogeneity between the trials was apparently substantial. Visual interpretation of forest plots for exercise tolerance measures, change in haemoglobin and LVEF showed the heterogeneity was influenced by outliers. Heterogeneity was most substantial for results of NYHA class ($p<0.0001$, I^2 = 96%) and this may be explained by inter-observer variability in judgement of NYHA class (Bennett 2002).

Results were based on published tabulated data. Although a comprehensive search strategy was conducted, there was evidence of publication bias in the change in haemoglobin level analysis. Hence, the true benefit of ESAs to increase haemoglobin levels may be less than reported and poor response to ESA therapy is a potential concern. Resistance to ESA therapy has been reported in 5 to 10% of CKD patients (Johnson 2007) and 40 to 50% of cancer patients (Beguin 2002). CKD patients requiring higher doses of ESA have higher levels of inflammatory markers (Smrzova 2005). CHF patients also have high levels of pro-inflammatory markers (Levine 1990) and resistance to the effect of endogenous EPO has been suggested. A study of 74 CHF patients (NYHA class III or IV) found endogenous EPO levels to be higher than expected for the degree of anaemia present correlating with elevated levels of C-reactive protein (van der Meer 2008). Moreover, higher serum EPO levels were associated with increased mortality. Only one included study measured serum EPO levels in patients and found elevated levels (Mancini 2003). These associations should be further researched and resistance to ESA therapy defined in the CHF setting.

Regarding external validity, participants had stable CHF, although co-morbidities were variably reported. The mean age of patients in the studies was over 70 years, similar to the age of CHF patients in the general population. In contrast, the mean age of participants

enrolled in ACE inhibitor trials was 61 years (Flather 2000) and 63 years with digoxin (DIG 1997).

The included studies were of short duration and insufficient to fully assess the effects of ESAs on CHF progression, mortality risk or adverse effects. Moreover, small sample sizes may have underpowered the overall effect. Two studies had several treatment arms (Cleland 2005; van Veldhuisen 2007), resulting in more participants in the ESA group. Longer-term larger trials of larger cohorts are required to examine the effect of ESAs on clinical outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Despite the limitations of this systematic review, we have found evidence to suggest that ESAs may improve anaemia and provide clinical benefits when added to routine CHF therapy to those in mild to moderately-anaemic patients with symptomatic CHF. Specifically, ESAs appear to improve exercise tolerance, increase cardiac function and relieve symptoms when dosed to haemoglobin levels ranging from 11.5 to 15g/dL. There is also evidence for an apparent reduction in morbidity and mortality, although confirmation will require trials of greater duration and sample size. The question of whether ESAs affect the risk of adverse effects in CHF remains unanswered, although we did not identify any significant increase in these outcomes in patients treated with ESAs.

Implications for research

Several questions deserve further investigation. The criteria for anaemia in CHF should be determined as CHF patients with subnormal haemoglobin levels are frequently undetected. As part of the criteria, an algorithm for the initial evaluation of anaemia in CHF should be developed, taking into account haemodilution, renal dysfunction and iron-deficiency assessment. There is a need to determine the mechanisms by which ESAs affect cardiac function, for example the improvement in anaemia and any direct actions on cardiomyocytes. Potential for resistance to ESA therapy warrants monitoring of baseline parameters (e.g. haemoglobin levels, iron parameters, inflammatory markers and serum EPO levels) in future studies to understand the dose-response relationship. The interaction between ESAs and iron therapy should be quantified to ensure optimal dosing regimes. In addition, the interaction between ESA treatment with routine CHF medication should be addressed, beginning with clear documentation of concurrent medication and comorbidities. Of considerable importance is clarifying the issues of benefit on mortality and adverse effects. Although the RED-HF trial should provide answers in terms of effects on mortality and morbidity, the optimal haemoglobin level for ESA therapy has yet to be addressed.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cleland 2005

Methods	Two sub-studies (Study 198 and Study 262) were reported in the paper. No data from Study 262 was used in the meta-analysis due to the crossover design Study 198: 2 months, randomised, double blind, placebo-controlled, 4-armed; Withdrawals: none
Participants	Study 198: 24 CHF patients; mean age: ESA 72 years, control 74 years; NYHA class II-IV; LVEF: ESA 36%, control 28%; Hb: ESA 11.0-12.1g/dL, control 11.5g/dL; Creatinine clearance: ESA 43-68mL/min, control 41mL/min
Interventions	Study 198: Treatment: darbepoetin alfa, 2.0, 3.0 or 5.0μg/kg every month (no target); Iron administered: none; Control: placebo (no iron)
Outcomes	Study 198: Primary outcomes: pharmacokinetic parameters, change in Hb. Secondary outcomes: number of adverse events.
Notes	Study 198: Single-centred. Only CHF patients were included in the analysis. Data could only be extracted from the 2.0μg/kg group for the 'Change in Hb level' outcome as data from other dosage groups were not suitable for meta-analysis. Declared pharmaceutical company sponsorship

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not reported.
Allocation concealment?	Unclear risk	Not reported.
Blinding? Subjective outcomes	Unclear risk	Quote: "darbepoetin alfa or placebo on study days 1 and 29". Comment: Placebo controlled.
Incomplete outcome data addressed? All outcomes	Unclear risk	Exclusions and withdrawals not reported.
Free of selective reporting?	High risk	All outcomes reported in the pre-specified way. Plasma BNP, LVEF and NYHA class were measured but not reported in results
Free of other bias?	Low risk	Appears to be free of other bias.

Cosyns 2008

Methods	2 months, randomised, controlled, blinding not reported. Withdrawals: not reported
Participants	28 patients; mean age: 68 years; 61% male NYHA class: (mean) III-IV LVEF: ESA 31%, control 30% Hb: ESA 10.1g/dL, control 10.3g/dL Creatinine clearance < 45mL/min
Interventions	Treatment: erythropoietin Iron administered: not reported Control: no treatment
Outcomes	Primary outcomes: NYHA class, change in Hb, LV parameters, degree of mitral regurgitation
Notes	Single-centred, reported as a Letter to the Editor.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not reported.
Allocation concealment?	High risk	Quote: "Fourteen were randomly assigned to receive EPO therapy and the remaining 14 served as control patients." Comment: Probably not done.
Blinding? Subjective outcomes	Unclear risk	Trial was not placebo-controlled and blinding was not reported
Incomplete outcome data addressed? All outcomes	Unclear risk	Withdrawals not reported. Study reported as a Letter to the Editor
Free of selective reporting?	Unclear risk	Outcomes not prespecified. Study reported as a Letter to the Editor
Free of other bias?	Unclear risk	Study reported as a Letter to the Editor.

Ghali 2008

Methods	52 weeks, randomised, double-blind, placebo-controlled Withdrawals: Treatment (40), control (44)
Participants	319 patients; mean age: ESA 68 years, control 69 years; 63% male NYHA class I-IV LVEF: ESA 35%, control 36%

Ghali 2008 (*Continued*)

	Hb: ESA 11.5g/dL, control 11.3g/dL Serum creatinine: ESA 1.5mg/dL, control 1.4mg/dL
Interventions	Treatment: darbepoetin alfa, starting dose 0.75μg/kg, every 2 weeks to target Hb of 13-15g/dL Iron administered: elemental iron orally, daily Control: placebo and iron
Outcomes	Primary outcomes: exercise duration (treadmill) Secondary outcomes: NYHA class improvement, quality of life (MLHFQ, PGA), time to death by any cause or first CHF hospitalisation
Notes	Multi-centred. Declared pharmaceutical company sponsorship.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "The randomization scheme was computer-generated, and stratified by study center."
Allocation concealment?	Low risk	Quote: "The randomization scheme was centrally-held."
Blinding? Subjective outcomes	Low risk	Quote: "Patients and personnel at the study site were blinded to the treatment. Darbepoetin alfa or matching placebo was provided in single-dose vials. To maintain the blind, doses were adjusted in a similar fashion for placebo patients on the basis of hemoglobin modeling data... To maintain the blind, daily elemental oral iron was administered."
Incomplete outcome data addressed? All outcomes	Low risk	Withdrawals and reasons reported.
Free of selective reporting?	Low risk	All outcomes reported in the pre-specified way.
Free of other bias?	Low risk	Appears to be free of other bias.

Kourea 2008a

Methods	3 months, randomised, single-blind, placebo-controlled Withdrawals: not reported
Participants	41 patients; mean age: ESA 73 years, control 65 years; 76% male NYHA class II-III LVEF: ESA 26%, control 28% Hb: ESA 10.9g/dL, control 11.4g/dL Serum creatinine: ESA 1.7mg/dL, control 1.7mg/dL
Interventions	Treatment: darbepoetin alfa, starting dose 1.5µg/kg, every 20 days to target Hb of 12.5-14g/dL Iron administered: iron sulphate 250mg orally, twice daily Control: placebo and iron
Outcomes	Primary outcomes: quality of life (KCCQ, DASI) Secondary outcomes: emotional stress (BDI, Zung SDS), exercise capacity (6MWT), plasma BNP
Notes	Single-centred

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "patients were randomized". Comment: Probably done as another study from the same investigators (Parissis 2008) describes use of computer randomization.
Allocation concealment?	Unclear risk	Not reported.
Blinding? Subjective outcomes	High risk	Quote: "single-blind", "all questionnaires were evaluated by staff who were blinded to the treatment status of individual patients" Comment: Patients were not blinded to treatment.
Incomplete outcome data addressed? All outcomes	Unclear risk	No attrition and exclusions reported.
Free of selective reporting?	Low risk	Published report includes all expected outcomes.
Free of other bias?	Low risk	Appears to be free of other bias.

Mancini 2003

Methods	3 months (or until haematocrit 45%), randomized, single blind, placebo-controlled Withdrawals: 2 (ESA), 1 (control)
Participants	23 patients; mean age: ESA 87 years, control 63 years; 78% male NYHA class III-IV LVEF: ESA 24%, control 21% Hb: ESA 11.0g/dL, control 10.9g/dL Serum creatinine: ESA 1.6mg/dL, control 1.6mg/dL
Interventions	Treatment: erythropoietin, 5000U thrice-weekly to target Hct of 45% and folate 1mg orally daily Iron administered: ferrous gluconate 325mg orally, daily Control: placebo (no iron)
Outcomes	Primary outcomes: exercise capacity (bicycle, 6MWT, peak VO2) Secondary outcomes: forearm vasodilatory function, Hb change, quality of life (MLHFQ, PGA)
Notes	Single-centred

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not reported.
Allocation concealment?	Unclear risk	Not reported.
Blinding? Subjective outcomes	High risk	Quote: "at the start of the study each control subject received an injection of normal saline. The investigators were not blinded to the study" Comment: Single-blind study. Also, control group did not receive iron or folate treatment
Incomplete outcome data addressed? All outcomes	Low risk	Withdrawals and reasons reported.
Free of selective reporting?	High risk	All outcomes reported in the pre-specified way. However standard deviations of quality of life scores were not reported
Free of other bias?	High risk	ESA group had much higher baseline VO2 and distance walked on 6-minute walk test

Palazzuoli 2006

Methods	12 months, randomized, double blind (3 months), open label (next 9 months), placebo-controlled Withdrawals: 0 (ESA), 2 (control)
Participants	38 patients; mean age: ESA 72 years, control 75 years; 61% male NYHA class III-IV LVEF: ESA 28.3%, control 28% Hb: ESA 10.4g/dL, control 10.6g/dL Serum creatinine: ESA 2.5mg/dL, control 2.4mg/dL
Interventions	Treatment: beta-EPO, 6000IU twice-weekly to target Hb of 11.5-12g/dL Iron administered: ferrous gluconate 300mg orally, daily Control: placebo and iron
Outcomes	Primary outcomes: not specified Secondary outcomes: NYHA class, renal function, exercise capacity (treadmill, peak VO2), plasma BNP
Notes	Single-centred

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were randomized but sequence generation was not reported
Allocation concealment?	Low risk	Comment: Pharmacy-controlled allocation was confirmed on author correspondence
Blinding? Subjective outcomes	Low risk	Quote: "[the control group] received the oral iron in the same daily dose and sc normal saline injections twice weekly", "EPO and saline injections were similar, and it was impossible to know which syringes the patients received. The physicians were unaware which syringes they used", "All physicians performing echocardiographic and exercise tests were blinded about the treatment" However blinding was stopped after initial 3 months.
Incomplete outcome data addressed? All outcomes	Low risk	Withdrawals and reasons reported.
Free of selective reporting?	Unclear risk	Primary outcomes not specified.

Palazzuoli 2006 (*Continued*)

Free of other bias?	Low risk	Appears to be free of other bias.

Palazzuoli 2007

Methods	12 months, randomized, double blind (4 months), open label (next 8 months), placebo-controlled Withdrawals: not reported
Participants	51 patients; mean age: ESA 74 years, control 72 years; 61% male NYHA class III-IV LVEF: ESA 30%, control 31% Hb: ESA 10.4g/dL, control 10.6g/dL Serum creatinine: ESA 2.5mg/dL, control 2.4mg/dL
Interventions	Treatment: beta-EPO, 6000IU twice-weekly to target Hb of 12-12.5g/dL Iron administered: ferrous gluconate 300mg orally, daily Control: placebo and iron
Outcomes	Primary outcomes: left ventricular dimensions and systolic function Secondary outcomes: cardiac events (sudden death, hospitalisation, myocardial infarction), body weight, blood pressure changes, edema development, NYHA class
Notes	Single-centred, 23 patients previously participated in Palazzuoli 2006.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were randomized but sequence generation was not reported
Allocation concealment?	Low risk	Comment: Pharmacy-controlled allocation was confirmed on author correspondence
Blinding? Subjective outcomes	Low risk	Quote: "[the control group] received oral iron alone and subcutaneous saline injections twice weekly", "physicians were unaware which syringes they used", "echocardiographic readers were blinded to the subject sudy assignment and their laboratory data"
Incomplete outcome data addressed? All outcomes	Low risk	Two patients were excluded so it is assumed that all other patient contributed to the data

Palazzuoli 2007 (*Continued*)

Free of selective reporting?	Low risk	All prespecified outcomes were reported.
Free of other bias?	High risk	Statistical comparisons that are emphasised are within group and between group comparisons for some outcomes are not reported

Parissis 2008

Methods	3 months, randomized, single blind, placebo-controlled Withdrawals: not reported
Participants	32 patients; mean age: ESA 72 years, control 69 years; unknown% male NYHA class II-III LVEF: ESA 26%, control 28% Hb: ESA 11.0g/dL, control 11.4g/dL Serum creatinine: ESA 1.7mg/dL, control 1.8mg/dL
Interventions	Treatment: darbepoetin alfa, 1.5mg/kg every 20 days to target Hb of 14g/dL Iron administered: iron sulphate 125mg orally, twice daily Control: placebo and iron
Outcomes	Primary outcomes: LV and RV systolic and diastolic function Secondary outcomes: exercise capacity (6MWT), haematological parameters, plasma BNP
Notes	Single-centred

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "A computer-generated randomization process was followed."
Allocation concealment?	Unclear risk	Not reported.
Blinding? Subjective outcomes	High risk	Quote: "Single-blind study...All evaluations were conducted by staff who was blinded to the treatment status of individual patients."
Incomplete outcome data addressed? All outcomes	Low risk	Quote: "5 patients were excluded from the study because they were unable to perform a 6MWT, 2 patients were excluded because they were on NYHA class I, and 2 patients were excluded because of cancer diagnosis.

Parissis 2008 (*Continued*)

		" Comment: Exclusions were reported, attrition was not reported
Free of selective reporting?	Low risk	All prespecified outcomes were reported.
Free of other bias?	Low risk	Appears to be free of other bias.

Ponikowski 2007

Methods	26 weeks, randomized, double blind, placebo-controlled Withdrawals: 3 (ESA), 3 (control)
Participants	41 patients; mean age: ESA 70 years, control 72 years; 54% male NYHA class I-III LVEF $\leq$ 40% Hb: ESA 11.8g/dL, control 11.6g/dL Serum creatinine: ESA 1.32mg/dL, control 1.45mg/dL
Interventions	Treatment: darbepoetin alfa, 0.75mg/kg every 2 weeks to target Hb of 13-15g/dL Iron administered: elemental iron 200-300mg orally, daily Control: placebo and iron
Outcomes	Primary outcomes: exercise tolerance (peak VO2 adjusted for body weight) Secondary outcomes: absolute peak VO2, exercise duration (treadmill), Hb, NYHA class, quality of life (KCCQ, MLHFQ, PGA), BNP, body weight, on-study hospitalisations
Notes	Multi-centred. Declared pharmaceutical company sponsorship.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "the randomization sequence which was computer generated"
Allocation concealment?	Low risk	Quote: "the randomization sequence... was concealed from investigators throughout the study"
Blinding? Subjective outcomes	Low risk	Quote: "Patients and personnel at the study centres were blinded to the identity of the study drug, hematology results (except at baseline) and hormone markers. The central randomization coordinator calculated the dose and the volume of drug to be administered providing only information on the volume... central data assessment at the

Ponikowski 2007 (*Continued*)

		core laboratory."
Incomplete outcome data addressed? All outcomes	Low risk	Exclusions and withdrawals were reported with reasons.
Free of selective reporting?	High risk	All prespecified outcomes were reported. However, range rather than standard deviation for NYHA class improvement was reported
Free of other bias?	Low risk	Appears to be free of other bias.

Silverberg 2001

Methods	Mean study duration of 8.2 months, randomized, open-label, controlled Withdrawals: not reported
Participants	32 patients; mean age: ESA 75.3 years, control 72.2 years; 72% male NYHA class III-IV LVEF: ESA 30.8%, control 28.4% Hb: ESA 10.3g/dL, control 10.9g/dL Serum creatinine: ESA 1.7mg/dL, control 1.4mg/dL
Interventions	Treatment: erythropoietin, 4000U weekly to target Hb of >12.5g/dL Iron administered: ferric sucrose 200mg IV, every 2 weeks Control: no treatment
Outcomes	Primary outcomes: not specified Secondary outcomes: NYHA class, dose of furosemide, LVEF, serum creatinine, days in hospital
Notes	Single-centred

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Quote: "patients were randomised consecutively into two groups"
Allocation concealment?	Unclear risk	Not reported.
Blinding? Subjective outcomes	High risk	Control group were not given placebo, patients were not blinded to treatment
Incomplete outcome data addressed? All outcomes	Unclear risk	Exclusions and attrition not reported.

Silverberg 2001 (*Continued*)

Free of selective reporting?	High risk	Outcomes were not prespecified.
Free of other bias?	High risk	Follow up period was not specified and ranged from 5 to 12 months

van Veldhuisen 2007

Methods	26 weeks, randomised, double-blind, placebo-controlled, 3-armed Withdrawals: 14 (ESA), 7 (control)
Participants	165 patients; mean age: ESA 71 years, control 71 years; 58% male NYHA class I-IV LVEF: ESA 29%, control 27% Hb: ESA 11.5g/dL, control 11.4g/dL Serum creatinine: ESA 1.4mg/dL, control 1.5mg/dL
Interventions	Treatment: darbepoetin alfa, starting dose 0.75µg/kg or 50µg, every 2 weeks to target Hb of 13-15g/dL Iron administered: elemental iron 200mg orally, daily Control: placebo and iron
Outcomes	Primary outcomes: rate of rise of Hb (rise/ week) Secondary outcomes: LVEF, exercise tolerance (6MWT), NYHA class, quality of life (MLHFQ, KCCQ, PGA)
Notes	Multi-centred. Declared pharmaceutical company sponsorship.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "Randomization was done centrally by a computer-generated scheme"
Allocation concealment?	Low risk	Quote: "Investigators used a central interactive voice-response system to obtain a unique subject number for each subject."
Blinding? Subjective outcomes	Low risk	Quote: "Patients and personnel were blinded to investigational product."
Incomplete outcome data addressed? All outcomes	Low risk	Exclusions and attrition reported.
Free of selective reporting?	Low risk	All prespecified outcomes were reported.

Free of other bias?	Low risk	However large imbalance in diabetes (and smaller imbalance in beta-blockade)

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Besarab 1998	Parallel-group trial in haemodialysis patients with CHF or ischaemic heart disease randomised to a normal or subnormal haematocrit target for epoetin alfa therapy
Drueke 2006	Parallel-group trial in chronic kidney disease patients randomised to normal or subnormal Hb levels for epoetin beta therapy
Kirkpantur 2005	Patients did not have CHF. RCT on epoetin beta for blood pressure and left ventricular geometry in haemodialysis patients
Kourea 2008b	No outcomes of interest reported.
Li 2004	Patients were not randomised, assigned by alternation.
Silverberg 2000	Uncontrolled trial. First prospective study on treating anaemia in CHF. 26 patients, NYHA IV, were treated with EPO and IV iron
Silverberg 2003	Uncontrolled trial. Studied EPO and IV iron in 179 diabetic and non-diabetic CHF patients (NYHA III-IV) with mild-moderate chronic renal failure
Singh 2006	Parallel-group trial in chronic kidney disease patients randomised to high or low Hb targets for epoetin alfa therapy
Zilberman 2007	Uncontrolled trial on EPO and IV iron for sleep-related breathing disorders in CHF patients

BDI Beck Depression Inventory
BNP B-type natriuretic peptide
CHF chronic heart failure
DASI Duke's Activity Status Index
EPO erythropoietin
ESA erythropoiesis-stimulating agent
g/dL grammes per decilitre
Hb haemoglobin
Hct Haematocrit
IU International Unit
KCCQ Kansas City Cardiomyopathy Questionnaire
LV left ventricular
LVEF left ventricular ejection fraction
mg microgrammes

mg/dL milligrammes per decilitre
MLHFQ Minnesota Living with Heart Failure Questionnaire
NYHA New York Heart Association
PGA Patient's Global Assessment
Zung SDS Zung Self-rating Depression Scale
µg/kg microgrammes per kilogramme
6MWT six-minute walk test

Characteristics of ongoing studies *[ordered by study ID]*

RED-HF 2008

Trial name or title	RED-HF Trial - Reduction of Events With Darbepoetin Alfa in Heart Failure Trial
Methods	Randomized, double-blind, placebo-controlled
Participants	Estimated enrolment of 2600 patients; eligible age >18 years NYHA class II-IV, CHF of at least 3 months duration Hb: 9-12 g/dL LVEF $\leq$ 40% Serum creatinine $\leq$ 3.0 mg/dL
Interventions	Treatment: darbepoetin alfa, starting dose 0.75µg/kg every 2 weeks to target Hb of 13g/dL Iron administered: not reported Control: placebo
Outcomes	Primary outcomes: composite of time to death from any cause or first hospital admission for worsening CHF Secondary outcomes: time to death from any cause, time to cardiovascular death or first hospital admission for worsening CHF (whichever occurs first), quality of life at 6 months (KCCQ)
Starting date	June 2006
Contact information	Amgen Inc.
Notes	Multicentred, phase III trial

DATA AND ANALYSES

Comparison 1. ESA versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exercise duration (bike and treadmill; seconds)	4	362	Mean Difference (IV, Random, 95% CI)	96.82 [5.22, 188.42]
2 Distance on 6-minute walk (metres)	4	261	Mean Difference (IV, Random, 95% CI)	69.33 [16.99, 121.67]
3 Exercise tolerance (stratified)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Distance on six-minute walk (metres)	4	261	Mean Difference (IV, Random, 95% CI)	69.33 [16.99, 121.67]
3.2 Exercise duration (seconds)	4	362	Mean Difference (IV, Random, 95% CI)	96.82 [5.22, 188.42]
4 Peak VO2 (mL/kg/min)	3	102	Mean Difference (IV, Random, 95% CI)	2.29 [0.62, 3.95]
5 VO2 anaerobic threshold	2	61	Mean Difference (IV, Random, 95% CI)	2.92 [0.09, 5.75]
6 Change in haemoglobin level (g/dL)	11	782	Mean Difference (IV, Random, 95% CI)	1.98 [1.62, 2.35]
7 Change in haemoglobin level (g/dL), type of ESA	11	782	Mean Difference (IV, Random, 95% CI)	1.98 [1.62, 2.35]
7.1 Darbepoetin alfa	6	610	Mean Difference (IV, Random, 95% CI)	1.74 [1.28, 2.20]
7.2 Recombinant human erythropoietin (epoetin alfa, epoetin beta)	5	172	Mean Difference (IV, Random, 95% CI)	2.26 [1.71, 2.81]
8 NYHA functional class improvement	8	657	Mean Difference (IV, Random, 95% CI)	-0.73 [-1.11, -0.36]
9 Kansas City Cardiomyopathy Questionnaire (overall summary score)	3	247	Mean Difference (IV, Fixed, 95% CI)	4.60 [0.46, 8.75]
10 Kansas City Cardiomyopathy Questionnaire (clinical summary score)	3	247	Mean Difference (IV, Fixed, 95% CI)	7.10 [2.77, 11.43]
11 Minnesota Living With Heart Failure Questionnaire (total score)	3	462	Mean Difference (IV, Random, 95% CI)	-2.02 [-5.78, 1.73]
12 Patient's Global Assessment (reported improvement)	4	548	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.02, 1.32]
13 LVEF (%)	5	321	Mean Difference (IV, Random, 95% CI)	5.77 [2.43, 9.11]
14 B-type natriuretic peptide (pg/mL)	5	203	Mean Difference (IV, Fixed, 95% CI)	-226.99 [-322.68, -131.29]
15 CHF-related hospitalisations	9	734	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.44, 0.87]
16 All-cause mortality	10	764	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.37, 0.99]
17 Adverse effect: hypertension	9	741	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.67, 2.54]
18 Adverse effect: stroke	8	700	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.52, 4.70]
19 Adverse effect: myocardial infarction	9	732	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.31, 1.55]

20 Adverse effect: other thromboembolic effects	9	741	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.22, 1.88]

Analysis 1.1. Comparison 1 ESA versus control, Outcome 1 Exercise duration (bike and treadmill; seconds).

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 1 Exercise duration (bike and treadmill; seconds)

Study or subgroup	ESA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Ghali 2008	136	57.3 (111.1)	124	45.6 (126.4)		34.7 %	11.70 [-17.34, 40.74]
Palazzuoli 2006	20	468 (150)	18	360 (144)		26.2 %	108.00 [14.47, 201.53]
Ponikowski 2007	19	597 (235.38)	22	468 (243.902)		18.7 %	129.00 [-17.93, 275.93]
Mancini 2003	15	657 (119)	8	459 (172)		20.4 %	198.00 [64.46, 331.54]
Total (95% CI)	**190**		**172**			**100.0 %**	**96.82 [5.22, 188.42]**

Heterogeneity: $Tau^2 = 6067.48$; $Chi^2 = 12.02$, df = 3 (P = 0.01); $I^2 = 75\%$

Test for overall effect: Z = 2.07 (P = 0.038)

Analysis 1.2. Comparison 1 ESA versus control, Outcome 2 Distance on 6-minute walk (metres).

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 2 Distance on 6-minute walk (metres)

Study or subgroup	ESA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Kourea 2008a	21	274 (97)	20	204 (103)		25.0 %	70.00 [8.69, 131.31]
Mancini 2003	15	404.77 (77.42)	8	320.65 (122.83)		17.1 %	84.12 [-9.58, 177.82]
Parissis 2008	21	296 (87)	11	167 (99)		22.8 %	129.00 [59.67, 198.33]
van Veldhuisen 2007	110	34.2 (76.56)	55	11.4 (76.39)		35.1 %	22.80 [-1.94, 47.54]
Total (95% CI)	**167**		**94**			**100.0 %**	**69.33 [16.99, 121.67]**

Heterogeneity: $Tau^2 = 1874.99$; $Chi^2 = 9.94$, df = 3 (P = 0.02); $I^2 = 70\%$

Test for overall effect: Z = 2.60 (P = 0.0094)

Analysis 1.3. Comparison 1 ESA versus control, Outcome 3 Exercise tolerance (stratified).

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 3 Exercise tolerance (stratified)

Study or subgroup	ESA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Distance on six-minute walk (metres)							
Kourea 2008a	21	274 (97)	20	204 (103)		25.0 %	70.00 [8.69, 131.31]
Mancini 2003	15	404.77 (77.42)	8	320.65 (122.83)		17.1 %	84.12 [-9.58, 177.82]
Parissis 2008	21	296 (87)	11	167 (99)		22.8 %	129.00 [59.67, 198.33]
van Veldhuisen 2007	110	34.2 (76.56)	55	11.4 (76.39)		35.1 %	22.80 [-1.94, 47.54]
Subtotal (95% CI)	**167**		**94**			**100.0 %**	**69.33 [16.99, 121.67]**
Heterogeneity: Tau^2 = 1874.99; Chi^2 = 9.94, df = 3 (P = 0.02); I^2 =70%							
Test for overall effect: Z = 2.60 (P = 0.0094)							
2 Exercise duration (seconds)							
Ghali 2008	136	57.3 (111.1)	124	45.6 (126.4)		34.7 %	11.70 [-17.34, 40.74]
Mancini 2003	15	657 (119)	8	459 (172)		20.4 %	198.00 [64.46, 331.54]
Palazzuoli 2006	20	468 (150)	18	360 (144)		26.2 %	108.00 [14.47, 201.53]
Ponikowski 2007	19	597 (235.38)	22	468 (243.902)		18.7 %	129.00 [-17.93, 275.93]
Subtotal (95% CI)	**190**		**172**			**100.0 %**	**96.82 [5.22, 188.42]**
Heterogeneity: Tau^2 = 6067.48; Chi^2 = 12.02, df = 3 (P = 0.01); I^2 =75%							
Test for overall effect: Z = 2.07 (P = 0.038)							

Analysis 1.4. Comparison 1 ESA versus control, Outcome 4 Peak VO2 (mL/kg/min).

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

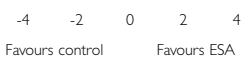
Comparison: 1 ESA versus control

Outcome: 4 Peak VO2 (mL/kg/min)

Study or subgroup	ESA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Mancini 2003	15	12.7 (2.8)	8	9.5 (1.6)		31.6 %	3.20 [1.40, 5.00]
Palazzuoli 2006	20	15.1 (2.8)	18	12 (2.5)		33.2 %	3.10 [1.41, 4.79]
Ponikowski 2007	19	12.4 (2.62)	22	11.7 (2.35)		35.2 %	0.70 [-0.83, 2.23]
Total (95% CI)	**54**		**48**			**100.0 %**	**2.29 [0.62, 3.95]**

Heterogeneity: $Tau^2 = 1.43$; $Chi^2 = 5.96$, df = 2 (P = 0.05); $I^2 = 66\%$

Test for overall effect: Z = 2.69 (P = 0.0071)



Analysis 1.5. Comparison 1 ESA versus control, Outcome 5 VO2 anaerobic threshold.

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

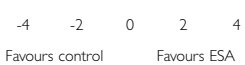
Comparison: 1 ESA versus control

Outcome: 5 VO2 anaerobic threshold

Study or subgroup	ESA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Mancini 2003	15	8.7 (1.9)	8	7.1 (0.8)		54.4 %	1.60 [0.49, 2.71]
Palazzuoli 2006	20	13.2 (3.6)	18	8.7 (2.7)		45.6 %	4.50 [2.49, 6.51]
Total (95% CI)	**35**		**26**			**100.0 %**	**2.92 [0.09, 5.75]**

Heterogeneity: $Tau^2 = 3.52$; $Chi^2 = 6.12$, df = 1 (P = 0.01); $I^2 = 84\%$

Test for overall effect: Z = 2.02 (P = 0.043)



Analysis 1.6. Comparison 1 ESA versus control, Outcome 6 Change in haemoglobin level (g/dL).

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

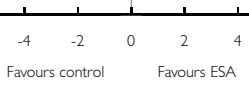
Comparison: 1 ESA versus control

Outcome: 6 Change in haemoglobin level (g/dL)

Study or subgroup	ESA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Cleland 2005	6	2.3 (0.6)	6	-0.4 (0.2)		10.0 %	2.70 [2.19, 3.21]
Cosyns 2008	14	13.1 (0.4)	14	10.2 (0.4)		11.4 %	2.90 [2.60, 3.20]
Ghali 2008	162	2.1 (1.11)	157	0.5 (1.11)		11.7 %	1.60 [1.36, 1.84]
Kourea 2008a	21	12.8 (1.4)	20	11.7 (1.5)		7.1 %	1.10 [0.21, 1.99]
Mancini 2003	15	14.3 (1.2)	8	11.5 (1.3)		5.9 %	2.80 [1.71, 3.89]
Palazzuoli 2006	20	11.6 (0.4)	18	9.8 (0.5)		11.4 %	1.80 [1.51, 2.09]
Palazzuoli 2007	26	12.4 (0.8)	25	10.5 (0.6)		10.8 %	1.90 [1.51, 2.29]
Parissis 2008	21	12.8 (1.3)	11	11.8 (1.3)		6.7 %	1.00 [0.05, 1.95]
Ponikowski 2007	19	13.9 (1.74)	22	12.3 (1.88)		5.8 %	1.60 [0.49, 2.71]
Silverberg 2001	16	12.9 (1.1)	16	10.8 (0.8)		8.7 %	2.10 [1.43, 2.77]
van Veldhuisen 2007	110	13.3 (1.2)	55	11.4 (1.4)		10.5 %	1.90 [1.47, 2.33]
Total (95% CI)	**430**		**352**			**100.0 %**	**1.98 [1.62, 2.35]**

Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 66.25$, df = 10 ($P<0.00001$); $I^2 = 85\%$

Test for overall effect: $Z = 10.64$ ($P < 0.00001$)



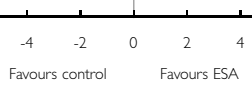
Analysis 1.7. Comparison 1 ESA versus control, Outcome 7 Change in haemoglobin level (g/dL), type of ESA.

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 7 Change in haemoglobin level (g/dL), type of ESA

Study or subgroup	ESA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Darbepoetin alfa							
Cleland 2005	6	2.3 (0.6)	6	-0.4 (0.2)		10.0 %	2.70 [2.19, 3.21]
Ghali 2008	162	2.1 (1.11)	157	0.5 (1.11)		11.7 %	1.60 [1.36, 1.84]
Kourea 2008a	21	12.8 (1.4)	20	11.7 (1.5)		7.1 %	1.10 [0.21, 1.99]
Parissis 2008	21	12.8 (1.3)	11	11.8 (1.3)		6.7 %	1.00 [0.05, 1.95]
Ponikowski 2007	19	13.9 (1.74)	22	12.3 (1.88)		5.8 %	1.60 [0.49, 2.71]
van Veldhuisen 2007	110	13.3 (1.2)	55	11.4 (1.4)		10.5 %	1.90 [1.47, 2.33]
Subtotal (95% CI)	**339**		**271**			**51.7 %**	**1.74 [1.28, 2.20]**
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 19.98$, df = 5 (P = 0.001); $I^2 = 75\%$							
Test for overall effect: Z = 7.38 (P < 0.00001)							
2 Recombinant human erythropoietin (epoetin alfa, epoetin beta)							
Cosyns 2008	14	13.1 (0.4)	14	10.2 (0.4)		11.4 %	2.90 [2.60, 3.20]
Mancini 2003	15	14.3 (1.2)	8	11.5 (1.3)		5.9 %	2.80 [1.71, 3.89]
Palazzuoli 2006	20	11.6 (0.4)	18	9.8 (0.5)		11.4 %	1.80 [1.51, 2.09]
Palazzuoli 2007	26	12.4 (0.8)	25	10.5 (0.6)		10.8 %	1.90 [1.51, 2.29]
Silverberg 2001	16	12.9 (1.1)	16	10.8 (0.8)		8.7 %	2.10 [1.43, 2.77]
Subtotal (95% CI)	**91**		**81**			**48.3 %**	**2.26 [1.71, 2.81]**
Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 32.05$, df = 4 (P<0.00001); $I^2 = 88\%$							
Test for overall effect: Z = 8.07 (P < 0.00001)							
Total (95% CI)	**430**		**352**			**100.0 %**	**1.98 [1.62, 2.35]**
Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 66.25$, df = 10 (P<0.00001); $I^2 = 85\%$							
Test for overall effect: Z = 10.64 (P < 0.00001)							



Analysis 1.8. Comparison 1 ESA versus control, Outcome 8 NYHA functional class improvement.

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 8 NYHA functional class improvement

Study or subgroup	ESA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Cosyns 2008	14	2.2 (0.5)	14	3.2 (0.4)		12.2 %	-1.00 [-1.34, -0.66]
Ghali 2008	142	-0.19 (0.4767)	128	-0.13 (0.4525)		13.4 %	-0.06 [-0.17, 0.05]
Kourea 2008a	21	2.2 (0.4)	20	2.7 (0.5)		12.6 %	-0.50 [-0.78, -0.22]
Palazzuoli 2006	20	2.8 (0.5)	18	3.6 (0.4)		12.5 %	-0.80 [-1.09, -0.51]
Palazzuoli 2007	26	2.7 (0.5)	25	3.5 (0.5)		12.6 %	-0.80 [-1.07, -0.53]
Parissis 2008	21	2.1 (0.5)	11	3.2 (0.6)		11.6 %	-1.10 [-1.51, -0.69]
Silverberg 2001	16	2.2 (0.7)	16	3.9 (0.3)		11.9 %	-1.70 [-2.07, -1.33]
van Veldhuisen 2007	110	-0.3 (0.6293)	55	-0.23 (0.5933)		13.1 %	-0.07 [-0.27, 0.13]
Total (95% CI)	**370**		**287**			**100.0 %**	**-0.73 [-1.11, -0.36]**

Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 132.21$, df = 7 ($P<0.00001$); $I^2 = 95\%$

Test for overall effect: Z = 3.83 (P = 0.00013)

Analysis 1.9. Comparison 1 ESA versus control, Outcome 9 Kansas City Cardiomyopathy Questionnaire (overall summary score).

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

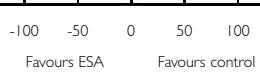
Outcome: 9 Kansas City Cardiomyopathy Questionnaire (overall summary score)

Study or subgroup	ESA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kourea 2008a	21	20 (20)	20	6 (14)		15.5 %	14.00 [3.47, 24.53]
Ponikowski 2007	19	12.4 (17)	22	10.4 (15.5)		17.1 %	2.00 [-8.02, 12.02]
van Veldhuisen 2007	110	8 (15.73)	55	4.9 (15.57)		67.3 %	3.10 [-1.96, 8.16]
Total (95% CI)	**150**		**97**			**100.0 %**	**4.60 [0.46, 8.75]**

Heterogeneity: Chi^2 = 3.66, df = 2 (P = 0.16); I^2 =45%

Test for overall effect: Z = 2.18 (P = 0.030)

Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1 ESA versus control, Outcome 10 Kansas City Cardiomyopathy Questionnaire (clinical summary score).

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 10 Kansas City Cardiomyopathy Questionnaire (clinical summary score)

Study or subgroup	ESA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kourea 2008a	21	21 (19)	20	2 (11)		21.0 %	19.00 [9.55, 28.45]
Ponikowski 2007	19	9.6 (15.1)	22	8.6 (17)		19.4 %	1.00 [-8.83, 10.83]
van Veldhuisen 2007	110	8.6 (17.83)	55	3.7 (17.06)		59.6 %	4.90 [-0.71, 10.51]
Total (95% CI)	**150**		**97**			**100.0 %**	**7.10 [2.77, 11.43]**

Heterogeneity: Chi^2 = 8.17, df = 2 (P = 0.02); I^2 =76%

Test for overall effect: Z = 3.22 (P = 0.0013)

Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 ESA versus control, Outcome 11 Minnesota Living With Heart Failure Questionnaire (total score).

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 11 Minnesota Living With Heart Failure Questionnaire (total score)

Study or subgroup	ESA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Ghali 2008	136	-9.3 (18.659)	120	-7.1 (20.813)		59.5 %	-2.20 [-7.07, 2.67]
Ponikowski 2007	19	-10.8 (22.1)	22	-13.7 (24.9)		6.8 %	2.90 [-11.49, 17.29]
van Veldhuisen 2007	110	-10.1 (19.9274)	55	-7.4 (20.024)		33.7 %	-2.70 [-9.17, 3.77]
Total (95% CI)	**265**		**197**			**100.0 %**	**-2.02 [-5.78, 1.73]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.50$, df = 2 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 1.05 (P = 0.29)

Analysis 1.12. Comparison 1 ESA versus control, Outcome 12 Patient's Global Assessment (reported improvement).

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 12 Patient's Global Assessment (reported improvement)

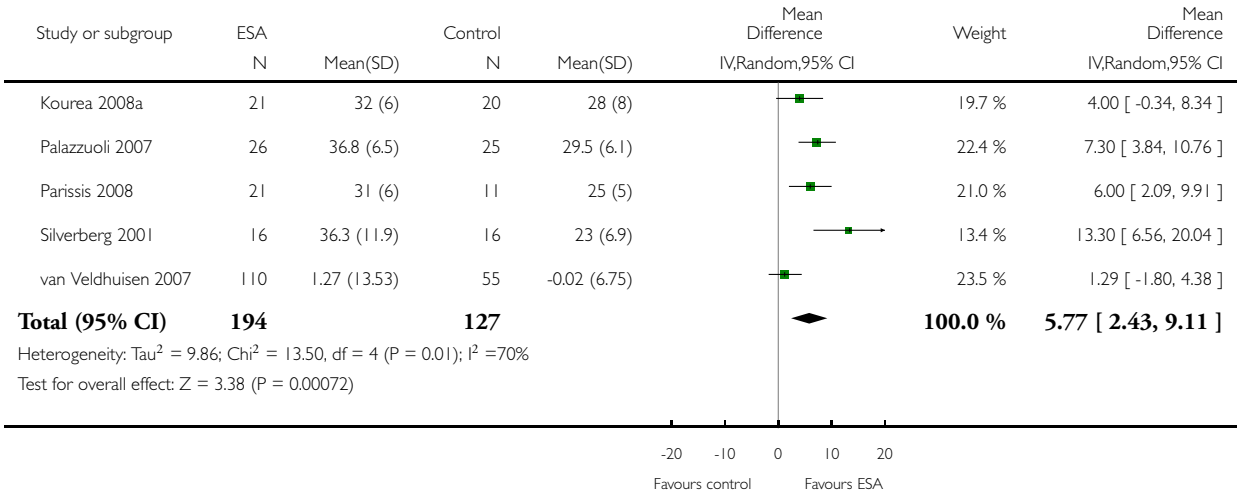
Study or subgroup	ESA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ghali 2008	115/162	112/157		71.4 %	1.00 [0.87, 1.14]
Mancini 2003	12/15	1/8		0.8 %	6.40 [1.01, 40.73]
Ponikowski 2007	15/19	9/22		5.2 %	1.93 [1.11, 3.36]
van Veldhuisen 2007	72/110	27/55		22.6 %	1.33 [0.99, 1.80]
Total (95% CI)	**306**	**242**		**100.0 %**	**1.16 [1.02, 1.32]**
Total events: 214 (ESA), 149 (Control)					
Heterogeneity: Chi^2 = 12.10, df = 3 (P = 0.01); I^2 =75%					
Test for overall effect: Z = 2.33 (P = 0.020)					

Analysis 1.13. Comparison 1 ESA versus control, Outcome 13 LVEF (%).

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 13 LVEF (%)



Analysis 1.14. Comparison 1 ESA versus control, Outcome 14 B-type natriuretic peptide (pg/mL).

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

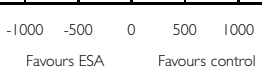
Outcome: 14 B-type natriuretic peptide (pg/mL)

Study or subgroup	ESA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kourea 2008a	21	517 (579)	20	1040 (851)		4.6 %	-523.00 [-970.69, -75.31]
Palazzuoli 2006	20	322 (187)	18	538 (246)		46.6 %	-216.00 [-356.11, -75.89]
Palazzuoli 2007	26	322 (187)	25	535 (346)		38.9 %	-213.00 [-366.50, -59.50]
Parissis 2008	21	661 (858)	11	1212 (821)		2.5 %	-551.00 [-1159.32, 57.32]
Ponikowski 2007	19	418.8 (269.4)	22	498.3 (787.6)		7.4 %	-79.50 [-430.20, 271.20]
Total (95% CI)	**107**		**96**			**100.0 %**	**-226.99 [-322.68, -131.29]**

Heterogeneity: $Chi^2 = 3.50$, df = 4 (P = 0.48); $I^2 = 0.0\%$

Test for overall effect: Z = 4.65 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1 ESA versus control, Outcome 15 CHF-related hospitalisations.

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 15 CHF-related hospitalisations

Study or subgroup	ESA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cleland 2005	3/18	0/6		1.0 %	2.58 [0.15, 43.86]
Ghali 2008	25/162	31/157		44.2 %	0.78 [0.48, 1.26]
Kourea 2008a	3/21	5/20		7.2 %	0.57 [0.16, 2.08]
Mancini 2003	1/15	4/8		7.3 %	0.13 [0.02, 1.00]
Palazzuoli 2006	4/20	8/18		11.8 %	0.45 [0.16, 1.24]
Palazzuoli 2007	4/26	8/25		11.5 %	0.48 [0.17, 1.40]
Parissis 2008	2/21	3/11		5.5 %	0.35 [0.07, 1.79]
Ponikowski 2007	2/19	3/22		3.9 %	0.77 [0.14, 4.14]
van Veldhuisen 2007	4/110	4/55		7.5 %	0.50 [0.13, 1.92]
Total (95% CI)	**412**	**322**		**100.0 %**	**0.62 [0.44, 0.87]**

Total events: 48 (ESA), 66 (Control)

Heterogeneity: $Chi^2 = 5.35$, df = 8 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 2.80 (P = 0.0051)

Analysis 1.16. Comparison 1 ESA versus control, Outcome 16 All-cause mortality.

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 16 All-cause mortality

Study or subgroup	ESA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cleland 2005	1/18	1/6		3.8 %	0.33 [0.02, 4.55]
Ghali 2008	11/162	18/157		46.9 %	0.59 [0.29, 1.21]
Kourea 2008a	1/21	3/20		7.9 %	0.32 [0.04, 2.80]
Mancini 2003	1/15	0/8		1.6 %	1.69 [0.08, 37.26]
Palazzuoli 2006	1/20	2/18		5.4 %	0.45 [0.04, 4.55]
Palazzuoli 2007	3/26	4/25		10.5 %	0.72 [0.18, 2.90]
Parissis 2008	0/21	2/11		8.3 %	0.11 [0.01, 2.09]
Ponikowski 2007	1/19	1/22		2.4 %	1.16 [0.08, 17.28]
Silverberg 2001	0/16	4/16		11.5 %	0.11 [0.01, 1.91]
van Veldhuisen 2007	6/108	0/55		1.7 %	6.68 [0.38, 116.43]
Total (95% CI)	**426**	**338**		**100.0 %**	**0.61 [0.37, 0.99]**
Total events: 25 (ESA), 35 (Control)					
Heterogeneity: Chi^2 = 6.68, df = 9 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 2.01 (P = 0.045)					

Analysis 1.17. Comparison 1 ESA versus control, Outcome 17 Adverse effect: hypertension.

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 17 Adverse effect: hypertension

Study or subgroup	ESA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cleland 2005	0/18	0/6			Not estimable
Ghali 2008	13/162	10/157		71.0 %	1.26 [0.57, 2.79]
Kourea 2008a	1/21	0/20		3.6 %	2.86 [0.12, 66.44]
Mancini 2003	0/15	0/8			Not estimable
Palazzuoli 2006	0/20	0/18			Not estimable
Palazzuoli 2007	0/26	0/25			Not estimable
Parissis 2008	1/21	0/20		3.6 %	2.86 [0.12, 66.44]
Ponikowski 2007	1/19	0/22		3.3 %	3.45 [0.15, 80.03]
van Veldhuisen 2007	2/108	2/55		18.5 %	0.51 [0.07, 3.52]
Total (95% CI)	**410**	**331**		**100.0 %**	**1.31 [0.67, 2.54]**

Total events: 18 (ESA), 12 (Control)

Heterogeneity: $Chi^2 = 1.77$, df = 4 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 0.79 (P = 0.43)

Test for subgroup differences: Not applicable

Analysis 1.18. Comparison 1 ESA versus control, Outcome 18 Adverse effect: stroke.

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 18 Adverse effect: stroke

Study or subgroup	ESA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cleland 2005	0/18	0/6			Not estimable
Ghali 2008	3/162	3/157		60.3 %	0.97 [0.20, 4.73]
Kourea 2008a	0/21	0/20			Not estimable
Mancini 2003	0/15	0/8			Not estimable
Palazzuoli 2006	1/20	0/18		10.4 %	2.71 [0.12, 62.70]
Palazzuoli 2007	2/26	1/25		20.2 %	1.92 [0.19, 19.90]
Ponikowski 2007	1/19	0/22		9.2 %	3.45 [0.15, 80.03]
van Veldhuisen 2007	0/108	0/55			Not estimable
Total (95% CI)	**389**	**311**		**100.0 %**	**1.57 [0.52, 4.70]**

Total events: 7 (ESA), 4 (Control)

Heterogeneity: $Chi^2 = 0.74$, df = 3 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 0.81 (P = 0.42)

Test for subgroup differences: Not applicable

Analysis 1.19. Comparison 1 ESA versus control, Outcome 19 Adverse effect: myocardial infarction.

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 19 Adverse effect: myocardial infarction

Study or subgroup	ESA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cleland 2005	0/18	0/6			Not estimable
Ghali 2008	4/162	5/157		36.7 %	0.78 [0.21, 2.83]
Kourea 2008a	0/21	1/20		11.1 %	0.32 [0.01, 7.38]
Mancini 2003	0/15	0/8			Not estimable
Palazzuoli 2006	1/20	2/18		15.2 %	0.45 [0.04, 4.55]
Palazzuoli 2007	2/26	3/25		22.1 %	0.64 [0.12, 3.52]
Parissis 2008	0/21	0/11			Not estimable
Ponikowski 2007	0/19	1/22		10.1 %	0.38 [0.02, 8.89]
van Veldhuisen 2007	2/108	0/55		4.8 %	2.57 [0.13, 52.60]
Total (95% CI)	**410**	**322**		**100.0 %**	**0.69 [0.31, 1.55]**

Total events: 9 (ESA), 12 (Control)

Heterogeneity: Chi^2 = 1.27, df = 5 (P = 0.94); I^2 =0.0%

Test for overall effect: Z = 0.89 (P = 0.37)

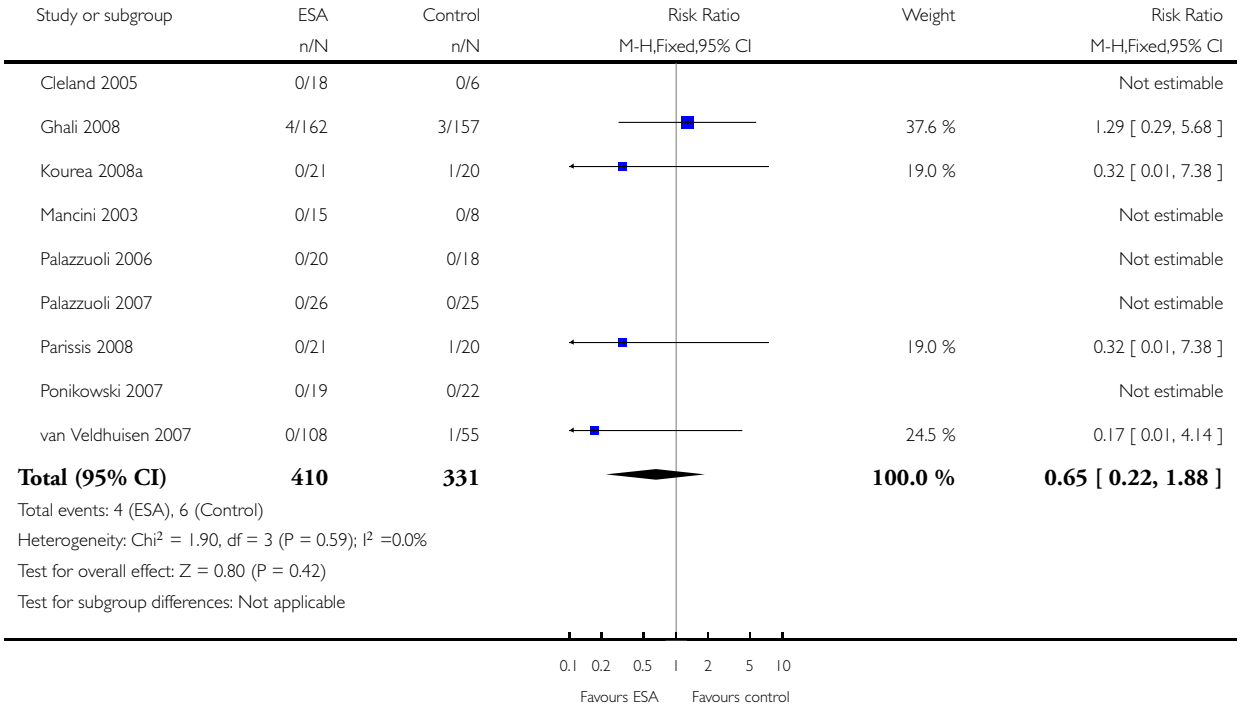
Test for subgroup differences: Not applicable

Analysis 1.20. Comparison 1 ESA versus control, Outcome 20 Adverse effect: other thromboembolic effects.

Review: Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients

Comparison: 1 ESA versus control

Outcome: 20 Adverse effect: other thromboembolic effects



ADDITIONAL TABLES

Table 1. Baseline characteristics of study participants.

Study	N	NYHA class	Age		LVEF (%)		Hb (g/dL)		Serum creatinine (mg/dL)	
			Control	ESA	Control	ESA	Control	ESA	Control	ESA
Cosyns 2008	28	III-IV	68*		30	31	10.3	10.1	†<45mL/min*	
Ghali 2008	319	I-IV	69	68	36	35	11.3	11.5	1.4	1.5

Table 1. Baseline characteristics of study participants. (*Continued*)

Kourea 2008a	41	II-III	65	73	28	26	10.4	10.9	1.7	1.7
Parissis 2008	32	II-III	69	72	28	26	11.4	11.0	1.8	1.7
Palaz-zuoli 2007	51	III-IV	72	74	31	30	10.6	10.4	2.4	2.5
Ponikowski 2007	41	I-III	72	70	≤40*		11.6	11.8	1.45	1.32
van Veld-huisen 2007	165	I-IV	71	71	27	29	11.4	11.5	1.5	1.4
Palaz-zuoli 2006	38	III-IV	75	72	28	28	10.6	10.4	2.4	2.5
Cleland 2005	24	II-IV	74	69	28	34	11.5	11.8	1.8*	
Mancini 2003	23	III-IV	63	87	21	24	10.9	11.0	1.6	1.6
Silver-berg 2001	32	III-IV	72	75	28	31	10.9	10.3	1.4	1.7
Ranges			63- 87		21- 36		10.1- 11.8		1.4- 2.5	

*= groups not specified, †= creatinine clearance

Table 2. Differing criteria for anaemia.

Study	Hb (g/dL) or Hct (%) criteria	Exclusion criteria				
		Acute or chronic bleed-ing	Iron deficiency	Vitamin B12 deficiency	Folate deficiency	Valvular disease
Cosyns 2008	<12g/dL	NS	NS	NS	NS	NS
Ghali 2008	9-12g/dL	Y	Y	Y	Y	Y

Table 2. Differing criteria for anaemia. (*Continued*)

Kourea 2008a	<12.5g/dL	Y	Y	Y	Y	NS
Parissis 2008	<12.5g/dL	Y	Y	Y	Y	NS
Palazzuoli 2007	<11.5g/dL	Y	NS	Y	Y	Y
Ponikowski 2007	9-12g/dL	NS	Y	NS	NS	NS
van Veldhuisen 2007	9-12g/dL	Y	Y	Y	Y	Y
Palazzuoli 2006	<11g/dL	Y	NS	Y	Y	Y
Cleland 2005	<12.5g/dL	NS	Y	Y	Y	Y
Mancini 2003	<35%	NS	Y	NS	NS*	NS
Silverberg 2001	10-11.5g/dL	Y	Y	Y	Y	NS

* = folate administered to patients, NS = not specified, Y = yes

APPENDICES

Appendix 1. Search strategies

The Cochrane Library

#1 MeSH descriptor heart failure explode all trees
#2 heart next failure in All Text
#3 cardiac next failure in All Text
#4 (#1 or #2 or #3)
#5 MeSH descriptor iron this term only
#6 MeSH descriptor iron compounds explode all trees
#7 MeSH descriptor Erythropoietin explode all trees
#8 MeSH descriptor Hematinics explode all trees
#9 iron in All Text
#10 ferrous in All Text
#11 ferric in All Text
#12 Erythropoiesis in All Text
#13 Erythropoietin in All Text
#14 epoetin in All Text
#15 Darbepoetin in All Text

#16 erythropoesis in All Text
#17 erythropoetin in All Text
#18 aranesp in All Text
#19 nesp in All Text
#20 epo All Text)
#21 rhuepo in All Text
#22 eprex in All Text
#23 ESA in All Text
#24 ESAs in All Text
#25 anti-anemi* in All Text
#26 anti-anaemi* in All Text
#27 antianemi* in All Text
#28 antianaemi* in All Text
#29 MeSH descriptor anemia explode all trees with qualifiers: TH,DH,DT
#30 darbopoetin in All Text
#31 darbepoietin in All Text
#32 epoietin in All Text
#33 epogen in All Text
#34 eprex in All Text
#35 neorecormon in All Text
#36 recormon in All Text
#37 anemi* in Record Title
#38 anaemi* in Record Title
#39 (#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14)
#40 (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23)
#41 (#24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32)
#42 (#33 or #34 or #35 or #36 or #37 or #38)
#43 (#39 or #40 or #41 or #42)
#44 (#4 and #43)

MEDLINE (Ovid)

1 exp Heart Failure/
2 heart failure.tw.
3 cardiac failure.tw.
4 or/1-3
5 Iron/
6 exp iron compounds/
7 exp Erythropoietin/
8 exp Hematinics/
9 iron.tw.
10 ferrous.tw.
11 ferric.tw.
12 Erythropoiesis.tw.
13 Erythropoietin.tw.
14 epoetin.tw.
15 Darbepoetin.tw.
16 Aranesp.tw.
17 Nesp.tw.
18 epogen.tw.
19 eprex.tw.
20 recormon.tw.
21 esa?.tw.

22 neorecormon.tw.
23 epoietin.tw.
24 darbepoietin.tw.
25 darbopoetin.tw.
26 epo.tw.
27 erythropoietin.tw.
28 erythropoiesis.tw.
29 epoietin.tw.
30 rhuepo.tw.
31 exp Anemia/dh, dt, th [Diet Therapy, Drug Therapy, Therapy]
32 anti-an?emi$.tw.
33 antian?emi$.tw.
34 or/5-33
35 4 and 34
36 randomized controlled trial.pt.
37 controlled clinical trial.pt.
38 Randomized controlled trials/
39 random allocation/
40 double blind method/
41 single-blind method/
42 or/36-41
43 exp animal/ not humans/
44 42 not 43
45 clinical trial.pt.
46 exp Clinical Trials as Topic/
47 (clin$ adj25 trial$).ti,ab.
48 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
49 placebos/
50 placebo$.ti,ab.
51 random$.ti,ab.
52 research design/
53 or/45-52
54 53 not 43
55 44 or 54
56 35 and 55

EMBASE (Ovid)

1 exp Heart Failure/
2 heart failure.tw.
3 cardiac failure.tw.
4 or/1-3
5 Iron/
6 Iron Derivative/
7 exp Antianemic Agent/
8 iron.tw.
9 ferrous.tw.
10 ferric.tw.
11 Erythropoiesis.tw.
12 Erythropoietin.tw.
13 epoetin.tw.
14 Darbepoetin.tw.
15 Aranesp.tw.

16 Nesp.tw.
17 epogen.tw.
18 eprex.tw.
19 recormon.tw.
20 esa?.tw.
21 neorecormon.tw.
22 epoietin.tw.
23 darbepoietin.tw.
24 darbopoetin.tw.
25 epo.tw.
26 erythropoietin.tw.
27 erythropoiesis.tw.
28 epoietin.tw.
29 rhuepo.tw.
30 exp Anemia/dt, th [Drug Therapy, Therapy]
31 anti-an?emi$.tw.
32 antian?emi$.tw.
33 or/5-32
34 4 and 33
35 controlled clinical trial/
36 random$.tw.
37 randomised controlled trial/
38 follow-up.tw.
39 double blind procedure/
40 placebo$.tw.
41 placebo/
42 factorial$.ti,ab.
43 (crossover$ or cross-over$).ti,ab.
44 (double$ adj blind$).ti,ab.
45 (singl$ adj blind$).ti,ab.
46 assign$.ti,ab.
47 allocat$.ti,ab.
48 volunteer$.ti,ab.
49 Crossover Procedure/
50 Single Blind Procedure/
51 or/35-50
52 34 and 51

WHAT'S NEW

Last assessed as up-to-date: 5 March 2009.

Date	Event	Description
10 December 2009	Amended	Minor typo error corrected in 'Results - Description of studies' section, under 'CHF-related hospitalisations'

CONTRIBUTIONS OF AUTHORS

All reviewers participated in preparation of the final review. Katherine Ngo, Marcus Flather and Julia Walters developed the concept. Katherine Ngo, Dipak Kotecha and Marcus Flather undertook data collection from the source papers, data analysis and interpretation. Julia Walters and Dipak Kotecha provided statistical and methodological advice. Luis Manzano, Alberto Palazzuoli and Dirk van Veldhuisen provided clinical advice.

DECLARATIONS OF INTEREST

Luis Manzano - currently involved in the RED-HF trial (ongoing study).

Alberto Palazzuoli - author of two of the included studies.

Dirk van Veldhuisen - author of one of the included studies, member of the Executive Committee of the RED-HF trial (ongoing study), and has received research grants and lecture fees from Amgen.

Marcus Flather, Dipak Kotecha, Katherine Ngo, Julia Walters - none known.

SOURCES OF SUPPORT

Internal sources

- Clinical Trials and Evaluation Unit, Royal Brompton Hospital, UK.

Ongoing grant funding

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A post-hoc meta-analysis of serum B-type natriuretic peptide levels was conducted.

NOTES

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia [*drug therapy; etiology]; Heart Failure [*complications]; Hematinics [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans